

Targeting ferroptosis in metabolic dysfunction-associated steatotic liver disease: From mechanisms to cell type-specific therapeutic strategies (Review)

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Received August 5, 2026; Accepted September 29, 2026

DOI: 10.3892/ijmm.2026.6028

Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD) impacts >30% of the global population. Its progression to metabolic dysfunction-associated steatohepatitis and liver fibrosis is the primary determinant for cirrhosis and hepatocellular carcinoma. Ferroptosis depends on iron and is driven by lipid peroxidation and is involved in the development of MASLD. Effective anti-fibrotic agents remain an unmet clinical need. The present review aimed to summarize the metabolic environment in MASLD, which is characterized by lipid overload, iron dysregulation and oxidative stress, and its role in facilitating ferroptosis using a cell type- and disease stage-specific framework, integrating intercellular crosstalk and evidence grading for biomarkers and therapeutic agents, as well as knowledge gaps, such as the paucity of direct human evidence, unresolved spatiotemporal dynamics and the necessity for precision delivery systems. The present review positions ferroptosis as a key pathophysiological element in MASLD and a promising frontier for diagnostic and therapeutic innovation by combining mechanistic insight with translational perspectives.

Contents

1. Introduction
2. Molecular basis of ferroptosis in MASLD
3. Cell type-specific roles of ferroptosis in MASLD
4. Potential biomarkers and detection of ferroptosis in MASLD

5. Potential therapeutic strategies
6. Delivery platforms
7. Limitations
8. Conclusion

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), encompasses a spectrum of liver disorders ranging from steatosis to metabolic dysfunction-associated steatohepatitis (MASH), which can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Because of the global rise in metabolic risk factors such as obesity and type 2 diabetes (T2DM), MASLD affects >30% of the worldwide population and represents a notable public health burden (1-3). Among all histological features, the stage of liver fibrosis is the strongest independent predictor of adverse long-term outcomes (4,5). In the United States, resmetirom has been approved for MASH with stage F2-F3 fibrosis. However, further research is needed to evaluate its long-term efficacy, safety and optimal criteria for patient selection (6-8). More recently, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, received Food and Drug Administration approval in 2025 for non-cirrhotic MASH with F2-F3 fibrosis, making it the second approved pharmacotherapy for this condition. Several other agents are in late-stage development, including GLP-1-based multi-agonists, fibroblast growth factor 21 analogues, pan-peroxisome proliferator-activated receptor (pan-PPAR) agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors. Combination strategies are increasingly explored, although validated biomarkers of treatment response and long-term outcome data remain lacking (9,10). These advances have changed the clinical landscape of MASLD/MASH and underscore the need for mechanism-based therapeutic strategies. A deeper understanding of the principal drivers of MASLD is required to identify new therapeutic targets.

Hepatocyte death is a central event in MASLD pathogenesis. It directly causes liver injury and promotes inflammation and fibrosis (11,12). While apoptosis, necroptosis and pyroptosis have been extensively studied, ferroptosis has recently

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Key words: ferroptosis, metabolic dysfunction-associated steatotic liver disease, lipid peroxidation, biomarker, therapeutic agent

emerged as a distinct, metabolism-driven mechanism contributing to MASLD progression (13,14). First characterized in 2012, ferroptosis is an iron-dependent form of cell death that results from excessive peroxidation of polyunsaturated fatty acids (PUFAs) in membrane phospholipids (PLs) (12,15-17). Its regulation is complex and involves the interplay of iron metabolism, lipid homeostasis and redox homeostasis. Redox homeostasis is controlled by the glutathione (GSH)-GSH peroxidase 4 (GPX4) axis, as well as by the ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) and GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4) pathways (18-21). As the principal organ responsible for iron metabolism and metabolic balance, the liver is vulnerable to ferroptosis. In MASLD, iron homeostasis is typically disrupted and oxidative stress is elevated, creating an environment that favors ferroptosis (22-24).

Ferroptosis plays a key role in MASLD (25-27). Furthermore, blocking ferroptosis has been suggested as a method to reduce liver damage in MASLD (15,28,29). Also, the progression of fibrosis is influenced by hepatocyte ferroptosis. However, inducing ferroptosis in activated hepatic stellate cells (HSCs) may alleviate this process (27,30). These opposing observations highlight the need for a cell type-specific framework. The present study performed a literature search in PubMed (pubmed.ncbi.nlm.nih.gov/) from January 2012 to April 2026, using combinations of the terms including 'ferroptosis', 'MASLD', 'MASH', 'MAFLD', 'NAFLD', 'NASH', 'lipid peroxidation', 'GPX4', 'ACSL4', 'iron', 'biomarker' and 'therapy'. Reference lists of relevant reviews and original articles were screened manually. Only peer-reviewed, English-language articles were included; conference abstracts, editorials, and non-peer-reviewed preprints were excluded. Priority was given to high-quality mechanistic studies, clinical trials and reviews. The present study aimed to provide a cell type-specific therapeutic map to indicate when ferroptosis should be inhibited or induced, together with an evidence-graded assessment of biomarkers and therapeutics, as well as the challenges and opportunities for translating these findings into clinical practice.

2. Molecular basis of ferroptosis in MASLD

Lipid metabolism and MASLD. The enrichment of PUFAs in membrane PLs provides the necessary substrates for lipid peroxidation (22,31) (Fig. 1). Central to this process is acyl-CoA synthetase long-chain family member 4 (ACSL4), which is key to PUFA activation. In collaboration with lysophosphatidylcholine acyltransferase 3, ACSL4 esterifies FAs into membrane PLs, thereby increasing membrane susceptibility to peroxidation. ACSL4 activity is a well-recognized determinant of ferroptosis sensitivity and its inhibition confers substantial protection, making it a potential preclinical target for MASLD therapy (32-35). This pro-ferroptotic program is amplified by the protein kinase C β II-ACSL4 axis (36). Beyond these direct regulators, recent genome-wide clustered regularly interspaced short palindromic repeats screening has identified the TATA box binding protein associated factor RNA polymerase I subunit C (TAFIC) as an upstream epigenetic determinant of ferroptosis in MASLD (37). TAFIC is upregulated during disease progression and directly interacts with

SET domain-containing 1A to remodel histone methylation and acetylation, thereby enhancing ACSL4 expression. The resulting increase in ACSL4 promotes lipid peroxidation and sensitizes hepatocytes to ferroptosis (37). Conversely, incorporation of monounsaturated FAs (MUFAs) into PLs shifts the lipid composition toward ferroptosis resistance. This protective lipid remodeling is mediated by acyl-CoA synthetase long-chain family member 3 (ACSL3), which preferentially incorporates MUFAs into PLs and decreases susceptibility to lipid peroxidation (38,39). Membrane-bound O-acyltransferase domain-containing proteins 1 and 2 are key regulators of PL remodeling and modulate ferroptosis by increasing MUFA-PL while decreasing PUFA-PL levels (40). These findings have direct therapeutic implications, as non-specific manipulation of lipid metabolism may produce unintended effects. Future studies should include comprehensive lipidomic profiling to define the specific PL patterns that determine ferroptosis susceptibility in the liver in MASLD.

Iron metabolism and MASLD. Iron homeostasis comprises three interconnected compartments: Systemic/intestinal handling, macrophage/Kupffer cell (KC) recycling and hepatocyte iron homeostasis (27). At the systemic level, dietary iron is absorbed by enterocytes and exported into the circulation via ferroportin (FPN). Heparin binds FPN and promotes its internalization and degradation, thereby decreasing both intestinal iron absorption and iron release from macrophages and hepatocytes (41,42). The hepatic hepcidin/intestinal hypoxia-inducible factor-2 α pathway modulates iron absorption in response to systemic iron status (43). Heparin transcription is regulated by bone morphogenetic protein (BMP)/SMAD signaling in hepatocytes, with BMP6 serving as the key iron-responsive ligand and transmembrane serine protease 6 serving as a negative regulator (41,44-46). In inflammatory states, IL-6 activates STAT3, which directly stimulates hepcidin transcription (47,48). Elevated hepcidin promotes FPN degradation, thereby trapping iron within splenic and hepatic macrophages, duodenal enterocytes and hepatocytes (49). In MASLD, hepcidin levels are typically low relative to hepatic iron stores (50), although inflammatory signals may simultaneously stimulate hepcidin production. The relative contribution of hepcidin suppression vs. inflammation-driven hepcidin elevation may vary across disease stages and patient subgroups. For example, hepcidin suppression may predominate in earlier or less inflammatory disease, whereas inflammation-driven hepcidin induction may become more prominent in advanced disease and in patients with a higher inflammatory burden. Beyond the liver and intestine, the kidney contributes to systemic iron homeostasis by reabsorbing filtered iron and clearing hepcidin (51), although its specific role in MASLD remains to be defined.

KCs, liver-resident macrophages, recycle iron from senescent erythrocytes and export it back into the circulation via FPN. Under conditions of low hepcidin, this export is enhanced, contributing to the circulating iron pool. Conversely, when hepcidin is elevated, FPN is degraded and iron is retained within macrophages (49). In MASLD, dysregulated iron handling leads to iron accumulation in KCs. Iron-rich KCs exhibit phenotypical changes toward a pro-inflammatory and pro-fibrotic state during MASH progression (52). A recent

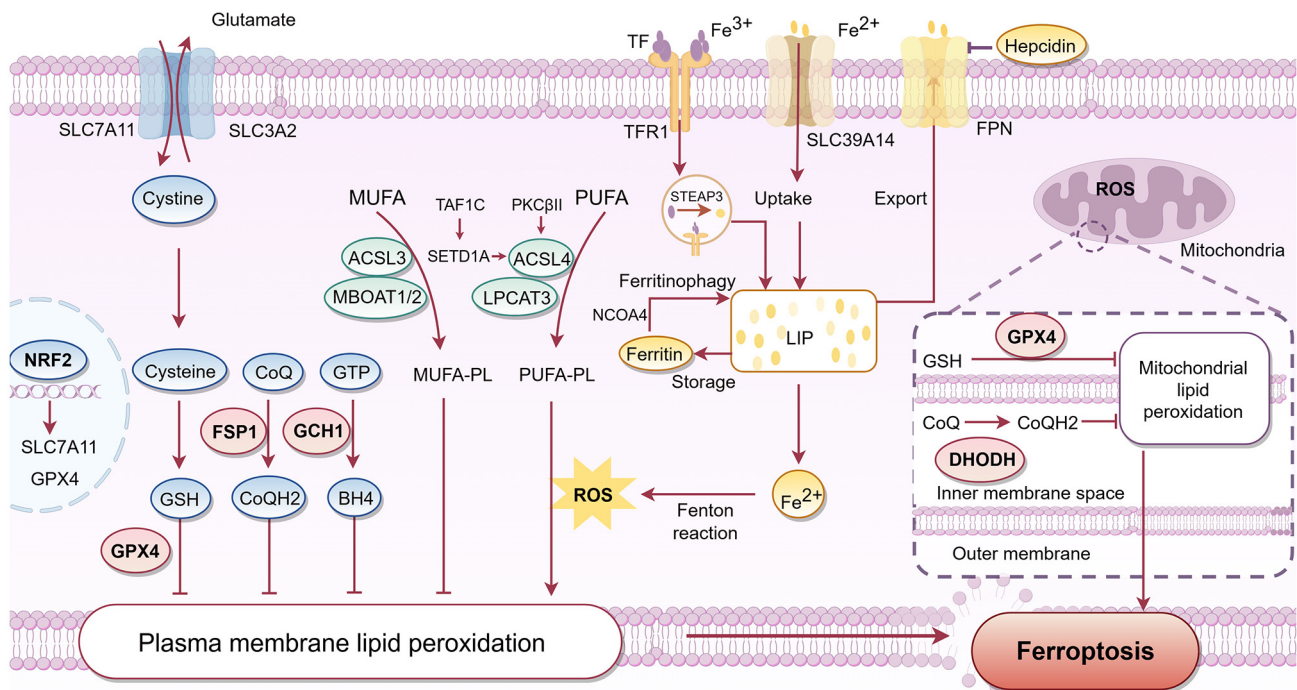


Figure 1. Molecular mechanisms regulating ferroptosis susceptibility in MASLD. PUFA esterification into membrane phospholipids by ACSL4 and LPCAT3 provides substrates for lipid peroxidation. MUFA incorporation via ACSL3 and MBOAT1/2 confers ferroptosis resistance. Iron enters hepatocytes through TFR1 or SLC39A14, is stored in ferritin and can be released into the LIP through ferritinophagy. In MASLD, hepcidin blocks iron export via ferroportin, leading to iron overload and oxidative damage. Antioxidant systems counteract these pro-ferroptotic effects, including the canonical GSH-GPX4 axis, the FSP1/CoQ10 pathway and the GCH1-BH4 axis. NRF2 is the primary transcriptional regulator for these. Mitochondria are both a notable source of ROS and a site of protection through mitochondrial GPX4 and DHODH. MASLD, metabolic dysfunction-associated steatotic liver disease; PUFA, polyunsaturated fatty acid; LPCAT, lysophosphatidylcholine acyltransferase; MBOAT, membrane-bound O-acyltransferase domain-containing protein; TFR, transferrin receptor; SLC39A14, ; LIP, labile iron pool; GSH, glutathione; GPX, glutathione peroxidase; FSP, ferroptosis suppressor protein; CoQ, coenzyme Q; GCH, GTP cyclohydrolase; BH, tetrahydrobiopterin; ROS, reactive oxygen species; DHODH, dihydroorotate dehydrogenase; TAF1C, TATA box-binding protein associated factor RNA polymerase I subunit C; SETD1A, SET domain-containing 1A; PKC, protein kinase C; MU, monounsaturated; PL, phospholipid; TF, transferrin; STEAP, six transmembrane epithelial antigen of prostate; NCOA, nuclear receptor coactivator; FPN, ferroportin.

study (53) identified neutrophil cytosolic factor (NCF)1 as a key regulator. Its upregulation in liver macrophages causes iron overload and ferroptosis in KCs. NCF1-induced oxidized PLs activate toll-like receptor (TLR)4-dependent hepatocyte hepcidin production, which increases iron deposition in KCs, forming a positive feedback loop that amplifies ferroptosis and MASH (53). Notably, not all hepatic macrophages experience iron overload in MASLD. Embryonic KCs exhibit decreased labile iron pools (LIPs) and mitochondrial dysfunction in MASH and KC-specific FPN knockout aggravates MASH (54). This highlights the heterogeneity of iron handling across macrophage populations.

Hepatocytes take up transferrin-bound iron via transferrin receptor 1. Within acidified endosomes, six transmembrane epithelial antigen of prostate 3 converts Fe^{3+} to Fe^{2+} , which is transported into the cytosol by solute carrier family 11 member 2 (SLC11A2) (55,56). Under iron overload conditions, uptake of non-transferrin-bound iron via SLC39A14 increases (57). Intracellularly, excess iron is sequestered in ferritin, which serves both as a reservoir and as a protective buffer against the Fenton reaction (58). When iron demand increases or oxidative stress rises, ferritin is selectively degraded through nuclear receptor coactivator 4-dependent ferritinophagy, releasing Fe^{2+} into the LIP (59,60). Expansion of the LIP facilitates ferroptosis by supplying the redox-active iron required for the Fenton reaction and subsequent lipid

peroxidation (61-63). The mitochondrial LIP acts as a major catalyst of Fenton reactions, generating reactive oxygen species (ROS) that trigger and sustain lipid peroxidation, thereby directly promoting ferroptosis (64-66). Iron efflux from hepatocytes is mediated by FPN, which is downregulated by hepcidin (41,42). These alterations in iron handling manifest as elevated serum ferritin concentrations and increased hepatic iron levels (67-69). Notably, a recent study (70) demonstrated that decreased FPN expression in hepatocytes leads to iron accumulation and systemic metabolic disturbance, identifying fetuin-A and leukocyte cell-derived chemotaxin 2 as key hepatokines. These findings are crucial for elucidating the association between MASLD and metabolic disorders and suggest therapeutic strategies such as hepatokine silencing, FPN overexpression or iron chelation (70). In addition, iron serves as a potent pro-oxidant, and its accumulation in the liver increases ROS production, lipid peroxidation and subsequent cell damage (71,72). The resulting oxidative stress and inflammation exacerbate the progression of liver fibrosis and cirrhosis, underscoring the key role of iron metabolism in MASLD pathogenesis (73).

Antioxidant systems and MASLD. Ferroptosis is controlled by antioxidant pathways, including the GSH-GPX4 axis, the FSP1/CoQ10 pathway and the GCH1-BH4 axis. These pathways are key for maintaining cell redox homeostasis and preventing

the accumulation of harmful lipid peroxides (74). Central to the GSH-GPX4 axis is the cystine/glutamate antiporter SLC7A11, which imports cystine, a key component for synthesizing GSH (75). GPX4 uses GSH to transform PL hydroperoxides into non-toxic lipid alcohols, thereby preventing ferroptosis (76). However, in MASLD, GSH depletion and GPX4 inactivation are typically observed (31). In parallel, FSP1 reduces CoQ10 to ubiquinol at the plasma membrane and other compartments, trapping lipid radicals independently of GSH (77,78). The GCH-BH4 axis also serves a key role in ferroptosis regulation. GCH1 and its metabolic derivative BH4 are involved in lipid remodeling that maintains the pool of PLs containing PUFA tails, counteracting their loss during ferroptosis and thereby conferring resistance to ferroptosis (79). NRF2 is key for orchestrating the antioxidant response and preventing ferroptosis. Upon activation, NRF2 upregulates genes associated with GSH synthesis and iron metabolism such as SLC7A11 and GPX4, protecting against oxidative stress and ferroptosis (80,81).

Mitochondrial dysfunction and MASLD. Mitochondrial dysfunction is a key feature of MASLD. Iron overload causes mitochondrial damage, characterized by increased ROS production and impaired mitochondrial respiration, which may exacerbate liver injury (82,83). Mitochondria are also involved in controlling ferroptosis. Mitochondrial ROS, particularly those derived from the electron transport chain (ETC), are key contributors to lipid peroxidation and ferroptosis (84,85), which are associated with mitochondrial metabolism. The tricarboxylic acid cycle and ETC maintain mitochondrial membrane potential and redox balance, which are essential for ferroptosis (86). Mitochondria also employ a key defense network against ferroptosis. Central to this system is the transport of GSH into the mitochondrial matrix, mediated by specific carrier proteins such as the dicarboxylate carrier and the oxoglutarate carrier. This import is required for the proper functioning of mitochondrial GPX4. Blocking these carriers increases ferroptosis by elevating mitochondrial ROS and depleting GSH (87). In addition, dihydroorotate dehydrogenase operates within the inner mitochondrial membrane, where it catalyzes the reduction of ubiquinone to ubiquinol, which directly mitigates lipid peroxidation independently of the GSH-GPX4 axis (88,89).

Collectively, the metabolic environment in MASLD is characterized by a lipid composition that permits ferroptosis, excess active iron and weakened antioxidant defenses. These factors increase the likelihood of ferroptosis (Fig. 1).

3. Cell type-specific roles of ferroptosis in MASLD

Hepatocyte ferroptosis. In MASLD, hepatocyte ferroptosis is a key contributor to liver inflammation and fibrosis (15,83,90). Studies highlight its role in amplifying oxidative stress and activating fibrogenic pathways (15,83,90). In particular, the accumulation of free FAs (FFAs) in hepatocytes is a hallmark of MASLD. This accumulation triggers lipid peroxidation and ferroptosis, thereby intensifying liver damage (91) (Fig. 2). Notably, another study demonstrated the protective role of activating transcription factor 4 in normal hepatocytes, where it maintains GSH production and inhibits ferroptosis-dependent inflammatory cell death (92).

Emerging evidence (93) suggests ferroptotic hepatocytes communicate with HSCs through exosome-mediated signaling. A recent study (93) showed that dietary cholesterol-induced downregulation of PPAR δ sensitizes hepatocytes to ferroptosis by modulating SLC7A11. Notably, exosomal double-stranded DNA (dsDNA) released from ferroptotic hepatocytes activates the stimulator of interferon genes (STING)/TANK-binding kinase 1/interferon regulatory factor 3 (IRF3) signaling pathway in HSCs, promoting the expression of profibrotic genes (93). This intercellular communication between hepatocytes and HSCs is reversed either by hepatocyte-specific overexpression of PPAR δ or by treatment with the selective PPAR δ agonist DN203316 (93). These findings underscore the role of PPAR δ as a key regulator of cholesterol-induced ferroptosis and highlight exosomal dsDNA/STING signaling as a key mediator linking hepatocyte ferroptosis with HSC-driven fibrogenesis.

In MASLD, decreased GPX4 levels are associated with increased vulnerability to ferroptosis, consequently enhancing hepatic oxidative stress and promoting fibrogenesis (15). Moreover, the vulnerability of hepatocytes to ferroptosis is modulated by immune-derived signals. Under intermittent hypoxia, a prevalent comorbidity in MASLD, IL-6 produced by macrophages induces upregulation of the E3 ubiquitin ligase membrane-associated RING finger protein 3 (MARCH3) in hepatocytes. MARCH3 facilitates ubiquitination and degradation of GPX4, increasing hepatocyte susceptibility to ferroptosis (94). Similarly, in MASH with T2DM, advanced glycation end product receptor 1 (AGER1) deficiency initiates hepatocyte ferroptosis and promotes epithelial-mesenchymal transition, thereby promoting fibrogenesis. Conversely, restoring AGER1 mitigates these effects (95). Collectively, hepatocyte ferroptosis serves a key role in the development of MASLD as it promotes oxidative stress, inflammation and fibrogenesis, thereby contributing to disease progression and complications.

HSC ferroptosis. HSCs are the primary cause of liver fibrosis, as their transdifferentiation into myofibroblasts leads to excessive extracellular matrix production (96). The role of ferroptosis in HSCs is context-dependent, with evidence pointing to opposing outcomes (97,98). Ferroptosis in HSCs can inhibit HSC activation and reduce liver fibrosis. On the other hand, ferroptosis-related programs in HSCs can exacerbate fibrogenesis. Quercetin (QG), the active compound in the Tibetan medicine Huang Tongluo Fang, induces ferroptosis in HSCs by promoting ubiquitin-proteasome-mediated degradation of GPX4. This is mediated by MARCHF8 and ultimately prevents HSC activation and reduces liver fibrosis (97). Conversely, other ferroptosis-related programs in HSCs promote fibrogenesis. Han *et al* (98) showed that acetyl-CoA acyltransferase 2 (ACAA2), a mitochondrial enzyme involved in FA β -oxidation, is markedly upregulated in HSCs during MASLD-associated fibrosis. ACAA2 undergoes palmitoylation, a modification that controls its subcellular localization and enhances ferroptosis-associated transcriptional programs, thereby exacerbating hepatic fibrosis. Inhibiting ACAA2 or blocking its palmitoylation attenuates both ferroptosis and fibrogenesis, an effect associated with AMP-activated protein kinase (AMPK) pathway activation and suppression of HSC activation (98).

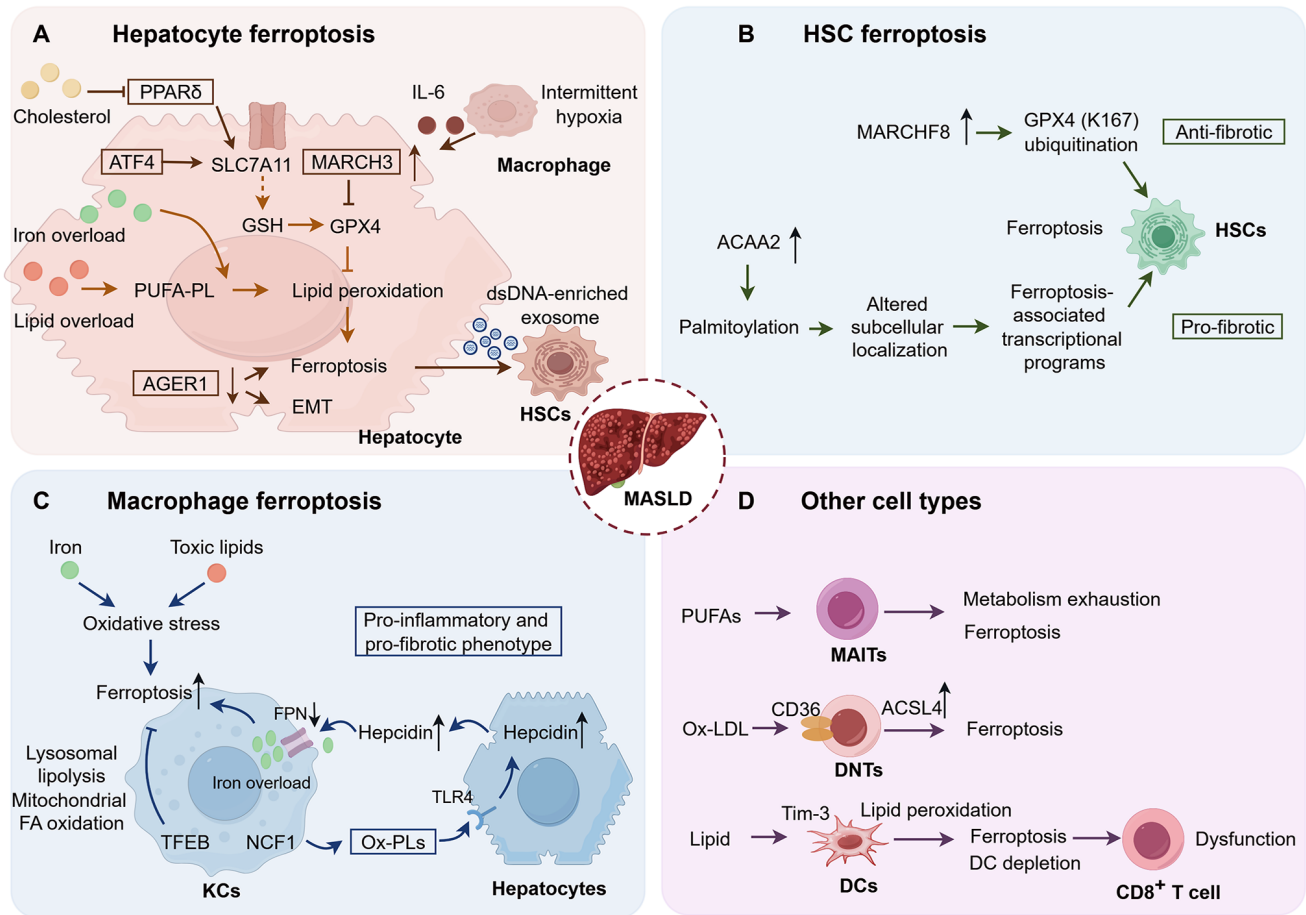


Figure 2. Cell type-specific ferroptosis in MASLD. (A) Hepatocyte ferroptosis may cause inflammation and fibrosis. (B) HSC ferroptosis is anti-fibrotic or pro-fibrotic depending on context. (C) KC ferroptosis is driven by NCF1 and amplified by a TLR4-hepcidin feedback loop, while TFEB protects KCs. (D) Other immune cells such as MAIT cells, DNTs and DCs also undergo ferroptosis, weakening anti-tumor immunity. MASLD, metabolic dysfunction-associated steatotic liver disease; HSC, hepatic stellate cell; KC, Kupffer cell; NCF, neutrophil cytosolic factor; TLR, toll-like receptor; TFEB, transcription factor EB; MAIT, mucosal-associated invariant T cell; DNT, double-negative regulatory T; DC, dendritic cell; ATF, activating transcription factor; MARCH, membrane-associated RING finger protein; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GPX, glutathione peroxidase; PUFA, polyunsaturated fatty acid; PL, phospholipid; AGER, advanced glycosylation end product-specific receptor; ds, double-stranded; EMT, epithelial-mesenchymal transition; ACAA, acetyl-CoA acyltransferase; FPN, ferroportin; Ox, oxidized; LDL, low-density lipoprotein; Tim, T cell immunoglobulin and mucin domain.

Rather than merely eliminating HSCs, ACAA2-driven ferroptosis triggers a pro-inflammatory and pro-fibrotic cascade, or occurs within a metabolic state that enhances fibrogenic signaling following cellular death. These divergent outcomes may be determined by several contextual factors, including the HSC activation state, disease stage, experimental model and local microenvironment. These observations demonstrate that inducing HSC ferroptosis cannot yet be regarded as a generally applicable antifibrotic strategy until the biological determinants governing its net tissue effect are defined.

KC ferroptosis. KCs are liver-resident macrophages that serve a key role in maintaining hepatic homeostasis and responding to liver injury (99). In MASLD, iron-rich KCs exhibit alterations associated with inflammation and fibrosis, such as upregulated CD11c and proinflammatory and profibrotic genes (Tnfa, Ccl3, and Timp1) and activation of MiT/TFE transcription factors (52). NCF1 is elevated in liver macrophages and dendritic cells (DCs) in patients with MASLD and in MASH mice. This upregulation promotes iron overload and ferroptosis in KCs, exacerbating MASH progression (53). Oxidized PLs released by macrophages activate TLR4-dependent

production of hepcidin in hepatocytes, which in turn increases iron accumulation in KCs and initiates ferroptosis (53). These findings suggest targeting NCF1 may improve KC function and limit MASH progression.

KCs exhibit abnormal lipid metabolism in MASLD, leading to the accumulation of toxic lipids and a pro-inflammatory state (100). Lipid-induced stress promotes ferroptosis and further contributes to liver injury. Importantly, induction of transcription factor EB in KCs protects against ferroptosis by enhancing lysosomal lipolysis and mitochondrial FA oxidation, decreasing oxidative stress and maintaining KC function (101). This highlights the potential of targeting lipid metabolism in KCs to prevent ferroptosis in MASLD.

Other types of immune cell. Beyond hepatocytes, HSCs and KCs, ferroptosis may also influence other liver cell populations; for example, accumulation of PUFAs in mucosal-associated invariant T (MAIT) cells causes ferroptosis-driven metabolic exhaustion, impairing their anti-tumor surveillance and accelerating disease progression (22). Similarly, oxidized low-density lipoprotein induces ferroptosis in double-negative regulatory T cells via CD36-mediated lipid uptake, decreasing

their survival and immunosuppressive capacity and thereby exacerbating liver inflammation (102).

DCs are the main antigen-presenting cells and are particularly susceptible to ferroptosis in MASLD. Li *et al* (103) demonstrated that, in MASLD-related HCC, a lipid-rich environment promotes lipid peroxidation and ferroptosis in DCs via a T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3)-dependent pathway. This depletes DCs, impairs CD8⁺ T cell response and facilitates tumor growth. Genetic or pharmacological inhibition of Tim-3 decreases lipid peroxidation, improves DC survival, reactivates CD8⁺ T cells and slows tumor growth. Tim-3 blockade enhances the efficacy of anti-PD-1 therapy and lenvatinib, achieving sustained tumor control in preclinical models (103,104). These findings identify Tim-3 as a key regulator of DC ferroptosis in metabolic liver disease.

A disease stage-specific framework may clarify when ferroptosis should be inhibited or induced. In early MASLD and in MASH with fibrosis, ferroptosis in hepatocytes and KCs is detrimental and should be inhibited. By contrast, selective induction of ferroptosis in activated HSCs may promote fibrosis resolution, although this strategy requires caution because HSC ferroptosis can be pro-fibrotic depending on context. During HCC progression, ferroptosis in immune cells such as DCs and MAIT and regulatory T cells impairs anti-tumor immunity. At this stage, protecting these immune cells or inducing ferroptosis specifically in malignant hepatocytes may be preferable. The consequences of ferroptosis vary by cell type and disease stage; therapeutic strategies should be designed accordingly.

4. Potential biomarkers and detection of ferroptosis in MASLD

A challenge in linking ferroptosis to MASLD is the lack of specific and tractable markers. At the tissue level, Cui *et al* (105) identified hyperoxidized peroxiredoxin 3 (PRDX3) as a direct ferroptosis marker in chronic liver diseases (Table I). In liver tissue sections, PRDX3 hyperoxidation is associated with disease severity (105), providing a tool for identifying ferroptotic lesions. This is valuable for staging MASLD. However, because it requires invasive tissue sampling, its use is confined to research settings and serial monitoring is not feasible.

Several studies (67,106-108) have therefore explored non- or less invasive strategies. In MASLD, serum ferritin is associated with hepatic iron burden and disease severity and may serve as a candidate stratification biomarker for iron chelation therapy (67). To the best of our knowledge, however, current evidence is limited to retrospective MASLD cohorts and MASH animal models, and its specificity for ferroptosis is confounded by systemic inflammation (109). In a large retrospective cohort of 7,333 patients with MASLD, metabolic hyperferritinaemia was associated with increased mortality and incident liver-associated events. It is also associated with cirrhosis-promoting alleles but not homeostatic iron regulator mutations. This suggests that hyperferritinaemia in MASLD reflects metabolic and genetic drivers rather than hereditary iron overload (106). Prospective validation in patients with MASLD is needed to determine whether ferritin can guide patient selection for iron chelation therapy or predict disease

progression. Breath volatile oxidized lipids (VOLs) offer a non-invasive approach, with levels elevated in patients with MASLD relative to healthy individuals (107). If confirmed in larger MASLD cohorts, this method may be used alongside serum markers. Yet the bioactivity of these VOLs remain unknown, and their specificity for hepatic ferroptosis vs. other sources of lipid peroxidation requires further investigation. Yang *et al* (108) investigated the association between ferroptosis-associated biomarkers and magnetic resonance imaging-derived parameters, such as T1 mapping and proton density fat fraction in MASLD-associated fibrosis. These findings suggest that specific imaging characteristics may serve as non-invasive indicators of ferroptosis activity, although these associations remain preliminary.

Extending molecular signatures toward clinical application, Matboli *et al* (110) adopted an integrated *in silico* and clinical approach. Using bioinformatic screening, molecular validation in serum samples from 400 participants and machine learning classification, the aforementioned study constructed a diagnostic model for MASLD/MASH that highlights the translational potential of ferroptosis- and exophagy-associated serum signatures. Nevertheless, this was a single-center cross-sectional study (110) and the specificity of these RNA signatures for ferroptosis remains to be established. In addition, a common genetic variant in mitochondrial amidoxime-reducing component 1 (rs2642438) is associated with altered ferroptosis susceptibility, suggesting that inherited genetic factors may serve as predictive biomarkers for ferroptosis-driven MASLD progression (111). However, its clinical utility as a predictive biomarker requires prospective validation.

5. Potential therapeutic strategies

Inhibiting hepatocyte ferroptosis. Recent studies have increasingly focused on inhibiting ferroptosis in hepatocytes as a strategy to decrease liver injury in MASLD (15,26,67). Several natural products and herbal formulations attenuate ferroptosis in MASLD models (112-114), although the strength of evidence varies (Fig. 3). Direct evidence of ferroptosis has been provided for a limited number of compounds, including betaine, plant sterol ester of α -linolenic acid, protocatechuic acid and arbutin. These compounds decrease erastin- or RAS-selective lethal 3-induced ferroptosis and modulate NRF2/GPX4 or fat mass and obesity-associated protein/SLC7A11 signaling in hepatocytes (115-118). By contrast, other natural products and herbal formulations including Hu Gan Tang, diosgenin, puerarin and gastrodin have primarily been shown to attenuate ferroptosis-associated molecular changes (112,119-121). For these compounds, the evidence supports an association with ferroptosis-related pathways rather than establishing ferroptosis as the causal mechanism. A common limitation of most natural products is the lack of information on oral bioavailability, tissue distribution and long-term safety, which hinders clinical translation. Additionally, many studies use the methionine-choline-deficient (or high-fat diet) models that do not fully recapitulate human MASLD (Table II) (113-114,122-127).

Clinically approved drugs with anti-ferroptotic properties have translation potential. Liraglutide improves MASLD in mouse models (128,129) by activating the AMPK/acetyl-CoA

Table I. Potential ferroptosis-associated biomarkers in MASLD.

Biomarker	Biological role	Clinical implication	Evidence type	(Refs.)
Hyperoxidized PRDX3	Direct marker of ferroptosis in liver tissue	Marker of ferroptotic damage in MASLD/MASH; associated with disease severity	Mouse/Huh7 human hepatoma cells	(105)
Serum ferritin	Iron storage protein	Elevated in MASLD; predicts response to iron chelation therapy	Human observational/mouse	(67)
Breath VOLs	Iron-driven lipid peroxidation products	Detectable in exhaled breath of patients with MASH; potential for non-invasive monitoring	Human observational/mouse	(107)
MRI T2*/R2*/PDFF	Non-invasive assessment of iron and fat	Associated with hepatic iron content and ferroptosis-associated gene expression	Rat/human dataset	(108)
Serum ferroptosis/exophagy-associated RNA signature	Key ferroptosis regulators	Multi-marker panel distinguishes MASH, MASLD and healthy controls	Human observational	(110)
MARC1 rs2642438 (p.A165T)	Mitochondrial enzyme; risk allele (p.A165) associated with higher ferroptosis and lipid content	Protective allele (p.T165) carriers show decreased ferroptosis and MASLD severity	Human observational/ <i>in vitro</i> (primary human hepatocytes)	(111)

MASLD, metabolic dysfunction-associated steatotic liver disease; PRDX3, peroxiredoxin 3; MASH, metabolic dysfunction-associated steatohepatitis; VOL, volatile oxidized lipid; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; MARC1, mitochondrial amidoxime reducing component 1.

carboxylase (ACC) pathway and attenuating ferroptosis-associated markers (129). Similarly, metformin, a first-line antidiabetic agent, mitigates hepatic iron overload via the AMPK/FPN pathway, reducing iron availability for Fenton reactions and lipid peroxidation (130). To the best of our knowledge, however, their anti-ferroptotic effects in MASLD have been demonstrated only in animal models, and clinical validation is lacking.

Tao *et al* (67) identified ferroterminator 1 (FOT1), a novel iron chelator, as an effective treatment for MASH. Analysis of clinical cohort and multiple mouse models (67,131) shows that hepatic iron overload contributes to MASH progression via the c-Myc/ACSL4 pathway and FOT1 ameliorates MASH in preclinical settings. Although serum ferritin predicted the response to FOT1 in clinical cohorts, FOT1 has not yet entered clinical trials for MASH (67). Liproxstatin 1 exerts hepatoprotective effects in a murine MASLD model, decreasing markers of steatosis, inflammation and fibrosis (28). Collectively, these findings support iron chelation as a promising strategy for ferroptosis-targeted therapy in MASLD, although clinical validation remains necessary. These direct ferroptosis-targeting agents may be particularly relevant for patients who do not achieve adequate response to approved therapies such as resmetirom or semaglutide. If serum ferritin or other iron-related markers can be used to identify a subpopulation with high ferroptosis burden, combining a ferroptosis inhibitor

or iron chelator with standard MASH therapy may be explored in future trials.

Targeting HSC ferroptosis. Although inhibiting ferroptosis in hepatocytes is key to limiting liver injury and MASLD progression, selectively inducing ferroptosis in activated HSCs may offer a strategy to reverse fibrosis. As aforementioned, QG induces ferroptosis in HSCs by promoting ubiquitination and degradation of GPX4, thereby decreasing collagen deposition in a MASLD mouse model (97). However, the effect of HSC ferroptosis depends on multiple factors, such as HSC activation state, disease stage and the local microenvironment. In addition, most preclinical studies on HSC ferroptosis in liver fibrosis use carbon tetrachloride or thioacetamide-induced models (132–138), which do not fully recapitulate the metabolic and inflammatory context of MASLD. Achieving cell type specificity also remains a challenge, and future work should focus on HSC-targeted delivery systems. Therefore, induction of HSC ferroptosis should not be regarded as a generally applicable antifibrotic strategy. Its therapeutic potential requires validation in more disease-relevant models before clinical translation.

Targeting macrophage ferroptosis. In a mouse model of MASH, baicalein, a traditional Chinese medicine extracted from *Scutellaria baicalensis*, improves metabolic dysfunction

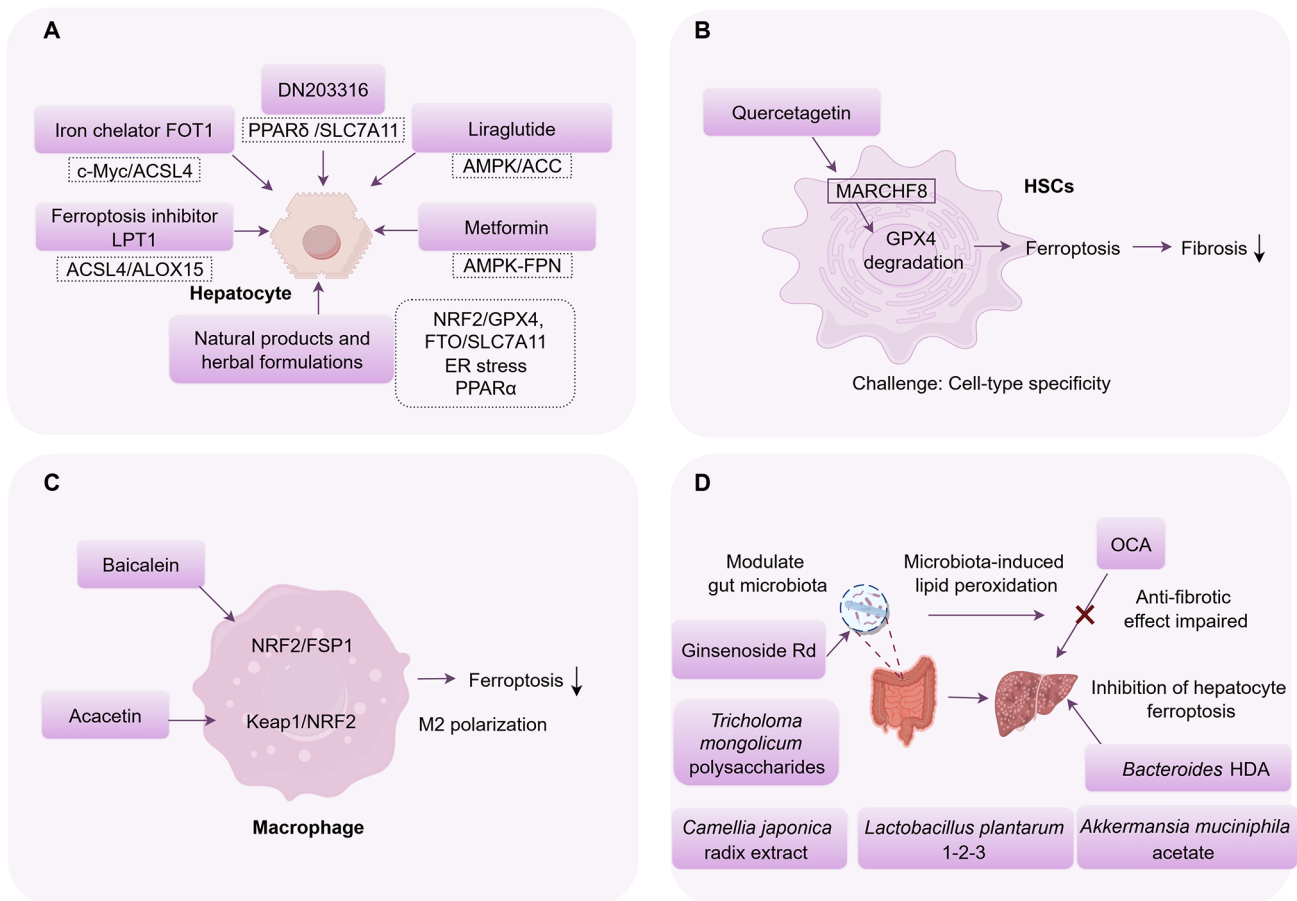


Figure 3. Potential therapeutic strategies targeting ferroptosis in metabolic dysfunction-associated steatotic liver disease. (A) Inhibition of hepatocyte ferroptosis by iron chelation, ferroptosis inhibitors, approved drugs and natural products. (B) Induction of HSC ferroptosis reverses fibrosis. (C) Targeting macrophage ferroptosis. (D) Modulating the gut-liver axis through probiotics, metabolites or herbal extracts. HSC, hepatic stellate cell; FOT, Ferroterminator1; ACSL, acyl-CoA synthetase long-chain family member; LPT, lipoxstatin-1; ALOX, arachidonate lipoxygenase; SLC7A11, solute carrier family 7 member 11; ACC, acetyl-CoA carboxylase; FPN, ferroportin; GPX, glutathione peroxidase; FTO, fat mass and obesity-associated protein; MARCH, membrane-associated RING finger protein; FSP, ferroptosis suppressor protein; OCA, obeticholic acid; HDA, hexadecanedioic acid.

and slows disease progression. Baicalein restores hepatic iron balance and decreases iron overload and lipid peroxidation (139,140). Its anti-ferroptotic effects have been confirmed in Raw264.7 macrophages exposed to FFAs (140). Mechanically, baicalein suppresses M1 macrophage polarization and promotes M2 polarization by activating the NRF2/FSP1 signaling pathway, thereby decreasing ferroptosis (140). Similarly, acacetin, a natural flavonoid, alleviates MASLD through mechanisms involving two distinct cell types: In hepatocytes, acacetin reduces Notch1-mediated lipogenesis and necroptosis; in macrophages, it blocks ferroptosis through the Keap1/NRF2 signaling pathway and promotes M2 polarization (141). These findings suggest targeting macrophage ferroptosis may represent a potential therapeutic strategy for MASLD.

Targeting the gut-liver axis. The gut microbiome serves a key role in the onset and progression of MASLD and its complications. Changes in microbiome composition are associated with disease progression and interventions targeting the microbiome can influence disease outcomes through several mechanisms, such as increasing gut permeability, decreasing levels of endotoxin-producing bacteria and modulating bile acid metabolism (142-146).

Recent studies (147-149) suggest that targeting the gut microbiome and its associated ferroptosis pathways may offer a therapeutic strategy for MASLD; for example, *Camellia japonica* radix extract modulates gut microbiota and linoleic acid metabolism, specifically targeting the pro-ferroptotic metabolite 9(S)-hydroperoxy-10E,12Z-octadecadienoic acid. This metabolite exerts a dual effect on Keap1 and SLC7A11, thereby regulating GPX4-mediated ferroptosis-associated signaling (147). Similarly, *Tricholoma mongolicum* polysaccharides alter gut microbiota composition and promote liver health (148). In addition, modulation of the gut microbiota by ginsenoside Rd (G-Rd) contributes to its protective effects against MASLD. G-Rd decreases the relative abundance of *Firmicutes* and the *Firmicutes/Bacteroidetes* ratio, both of which are typically elevated in MASLD. Furthermore, G-Rd lowers the abundance of *Faecalibaculum rodentium* while increasing that of *Muribaculum intestinale*. These alterations in gut microbiota composition regulate lipid metabolism and alleviate oxidative stress in the liver (149). The findings support an association with ferroptosis-associated pathways rather than establishing ferroptosis as the causal mechanism.

Metabolites from certain gut microbial strains directly or indirectly inhibit hepatic ferroptosis. For example, Zhang *et al* (150) demonstrated that hexadecanedioic acid,

Table II. Potential therapeutic strategies targeting ferroptosis in MASLD.

Agent/ intervention	Target cell	Target pathway/ mechanism	Model system	Evidence type	Disease stage	Effect on MASLD	(Refs.)
FOT1	Hepatocyte	Iron chelation; targets c-Myc/ACSL4 signaling	Mouse MASH; human	Preclinical; human observational	MASH	Inhibition	(67)
LPT1	Hepatocyte	Blocks ACSL4/ ALOX15 signaling; reduces lipid ROS, 4-HNE and MDA; inhibits PANoptosis	HFD mice with 30% fructose in water; hepatocytes	Preclinical	MASLD	Inhibition	(28)
PPAR δ agonist DN203316	Hepatocytes	Upregulates SLC7A11	MASH mice; human liver; hepatocytes/ HSCs	Preclinical; human observational	MASH with fibrosis	Inhibition	(93)
Betaine	Hepatocytes	Activates NRF2/ GPX4 signaling	HFD mice; AML12 cells	Preclinical	MASLD	Inhibition	(115)
Plant sterol ester of α -linolenic acid	Hepatocytes	Activates NRF2 signaling	HFD mice; HepG2 (OA/ erastin)	Preclinical	MASLD	Inhibition	(116)
Proto-catechuic acid	Hepatocytes	Regulates NRF2 signaling	HFD mice; MHCC97-H cells (erastin/ sorafenib)	Preclinical	MASLD	Inhibition	(117)
Arbutin	Hepatocytes	FTO/SLC7A11	HFD mice; HepG2 (erastin)	Preclinical	MASLD	Inhibition	(118)
Hu Gan Tang	Hepatocytes	Activates NRF2/ GPX4 signaling	Rat HFD model; HepG2	Preclinical	MASLD	Inhibition	(119)
Diosgenin	Hepatocytes	Nrf2-mediated oxidative stress regulation	Rat HFD model; hepatoma cells	Preclinical	MASLD	Inhibition	(120)
Puerarin	Hepatocytes	Upregulates SIRT1/ NRF2 signaling	HFD/STZ mice; AML12 cells	Preclinical	MASLD	Inhibition	(112)
Gastrodin	Hepatocytes	Regulates Keap1/ NRF2 signaling	HFD mice; HepG2 (PA/OA)	Preclinical	MASLD	Inhibition	(121)
Melatonin	Hepatocytes	Inhibits ER stress via the MT2/cAMP/PKA/ IRE1 signaling pathway	HFD mice; HepG2 (PA/ erastin)	Preclinical	MASLD	Inhibition	(122)
Curcumol	Hepatocytes	Inhibits the EGFR-ER stress axis	HFD mice; <i>in vitro</i>	Preclinical	MASLD	Inhibition	(123)
Lycorine	Hepatocytes	Decreases steatosis/ oxidative stress; intestinal homeostasis	HFD mice; HepG2 (PA)	Preclinical	MASLD	Inhibition	(114)
Si-Wu-Tang	Hepatocytes	Inhibits ACSL4-mediated arachidonic acid metabolism	MCD diet-fed mice	Preclinical	MASLD	Inhibition	(113)
Shugan Xiaozhi decoction	Hepatocytes	Regulates the p53/ SLC7A11/GPX4 pathway	MCD-induced MASH mice	Preclinical	MASH	Inhibition	(124)
Nuciferine	Hepatocytes	Activates PPAR α signaling	HFD/ApoE ^{-/-} mice; AML12 cells (RSL3)	Preclinical	MASLD	Inhibition	(125)

Table II. Continued.

Agent/ intervention	Target cell	Target pathway/ mechanism	Model system	Evidence type	Disease stage	Effect on MASLD	(Refs.)
Vitamin D	Hepatocytes	Modulates ferroptosis-associated pathways	HFD mice; HepG2 (PA)	Preclinical	MASLD	Inhibition	(126)
Chryindicolide O (from <i>Chrysanthemum indicum</i>)	Hepatocytes	Modulates SIRT1-mediated lipid accumulation	HFD zebrafish; AML12 cells (PA/OA)	Preclinical	MASLD/ steatosis	Inhibition	(127)
Liraglutide	Hepatocyte	Activates AMPK/ ACC	HFD/streptozotocin mice; HepG2/Hep3B/ PLC cells	Preclinical	T2DM-associated MASLD	Inhibition	(129)
Metformin	Hepatocytes	Activates AMPK-FPN, decreases iron overload	HFD rats; PA/ erastin-treated WRL68 cells	Preclinical	MASLD	Inhibition	(130)
Quercetin	Activated HSCs	MARCHF8-mediated GPX4 degradation	High-fat, high-cholesterol diet-induced MASH mouse model; primary mouse HSCs and LX-2 cells	Preclinical	MASH fibrosis	Induction (HSC ferroptosis)	(97)
Baicalein	Macrophage	Activates NRF2/FSP1 signaling; promotes M2 polarization	WD-fed MASH mice; FFA-treated Raw264.7 cells	Preclinical	MASH	Inhibition (macrophage ferroptosis)	(140)
Acacetin	Macrophage	Keap1/NRF2; promotes M2 polarization	HFD mice; RAW264.7/ BMDM/ AML12 cells	Preclinical	MASLD	Inhibition	(141)
<i>Camellia japonica</i> radix	Gut microbiota MASLD	Modulates 9(S)- HpODE/Keap1/SLC7 A11 signaling	Mouse MASLD model	Preclinical		Inhibition	(147)
<i>Tricholoma mongolicum</i> polysaccharides	Gut microbiota/ hepatocytes	Modulates gut microbiota-metabolite- ferroptosis axis	HFD mice; HL- 7702 cells	Preclinical	MASLD	Inhibition	(148)
G-Rd	Gut microbiota/ hepatocytes	Modulates gut microbiota composition	HFD mice	Preclinical	MASLD	Inhibition	(149)
Bacteroides HDA	Hepatocytes	Inhibits IRE1 α - XBP1s	Human MASLD cohort; HFD mice; HepG2 (erastin)	Preclinical; Human observational	MASLD	Inhibition	(150)
<i>Lactobacillus plantarum</i> 1-2-3	Gut micro biota/ hepatocytes	Regulates dysregulated lated FA metabolism	HFD mice; FFA-treated AML12 cells	Preclinical	MASLD	Inhibition	(151)

Table II. Continued.

Agent/ intervention	Target cell	Target pathway/ mechanism	Model system	Evidence type	Disease stage	Effect on MASLD	(Refs.)
Acetate from <i>Akkermansia muciniphila</i>	Hepatocytes	Activates hepatic AMPK/SIRT1/PGC- 1 α signaling	High-fat, high- fructose diet- induced MASLD mouse model; AML12/ HepG2 (erastin)	Preclinical	MASLD	Inhibition	(152)
Selenium NPs stabilized by <i>Ganoderma lucidum</i> spore poly- saccharides	Hepatocyte	Selenium antioxidant properties	HepG2 cells (PA)	Preclinical (<i>in vitro</i>)	MASLD	Inhibition	(155)
Biomimetic selenium nanocom- posites	Hepatocyte	Regulates lipid and iron homeostasis	Choline- deficient, L- amino acid- defined, high- fat diet induced MASH mice; L-02 cells (PA/OA)	Preclinical	MASH	Inhibition	(156)
GA receptor- targeted chitosan oligosac- charide NPs	Hepatocytes	GA receptor-mediated liver targeting; regulates GPX4/GSH; chelates Fe ²⁺	Tetracycline- induced MASLD mice; HepG2 cells	Preclinical	MASLD	Inhibition	(157)
Unified nanothera- peutic platform (FXR agonist, ferroptosis inhibitor, anti-fibrotic agent)	Hepatocytes, HSCs	Activates FXR; delivers liproxtatin-1; degrades extracellular matrix via NO	MCD-induced MASH mice	Preclinical (<i>in vivo</i>)	MASH	Inhibition	(158)
Hepatocyte- targeted hydrogen delivery	Hepatocytes	Fenton reaction inhibition	Choline- deficient, L-amino acid- defined, high fat diet-induced MASLD mice	Preclinical (<i>in vivo</i>)	MASLD	Inhibition	(159)
FTH1- enriched EVs	Hepatocytes	Delivers FTH1; restores iron homeostasis; upregulates Nrf2/GPX4; downregulates ACSL4	Human biopsies; MASLD mice; mouse primary hepatocytes/ HepG2	Preclinical; human tissue	MASLD	Inhibition	(160)

4-HNE, 4-hydroxynonenal; ACC, acetyl-CoA carboxylase; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX15, arachidonate 15-lipoxygenase; AMPK, AMP-activated protein kinase; ApoE^{-/-}, apolipoprotein E deficient; BMDM, bone marrow-derived macrophage; cAMP, cyclic adenosine monophosphate; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; EV, extracellular vesicle; FFA, free fatty acid; FPN, ferroportin; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FTO, fat mass and obesity-associated protein; FXR, farnesoid X receptor; GA, glycyrrhetic acid; GPX4, glutathione peroxidase 4; GSH, glutathione; HFD, high-fat diet; HSC, hepatic stellate cell; IRE1 α , inositol-requiring enzyme 1 alpha; Keap1, Kelch-like ECH-associated protein 1; LPT1, liproxtatin-1; M2, macrophage type 2; MARCHF8, membrane-associated RING-CH finger protein 8; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MCD, methionine-choline-deficient; MDA, malondialdehyde; MT2, melatonin receptor 2; NO, nitric oxide; NP, nanoparticle; NRF2, nuclear factor erythroid 2-related factor 2; OA, oleic acid; PA, palmitic acid; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; RSL3, Ras-selective lethal 3; SIRT1, sirtuin 1; SLC7A11, solute carrier family 7 member 11; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; WD, Western diet; XBP1, spliced X-box binding protein 1; 9(S)-HpODE, 9(S)-hydroperoxy-10E,12Z-octadecadienoic acid; FOT1, FerroTerminator1; G-Rd, ginsenoside Rd; HDA, hexadecanedioic acid.

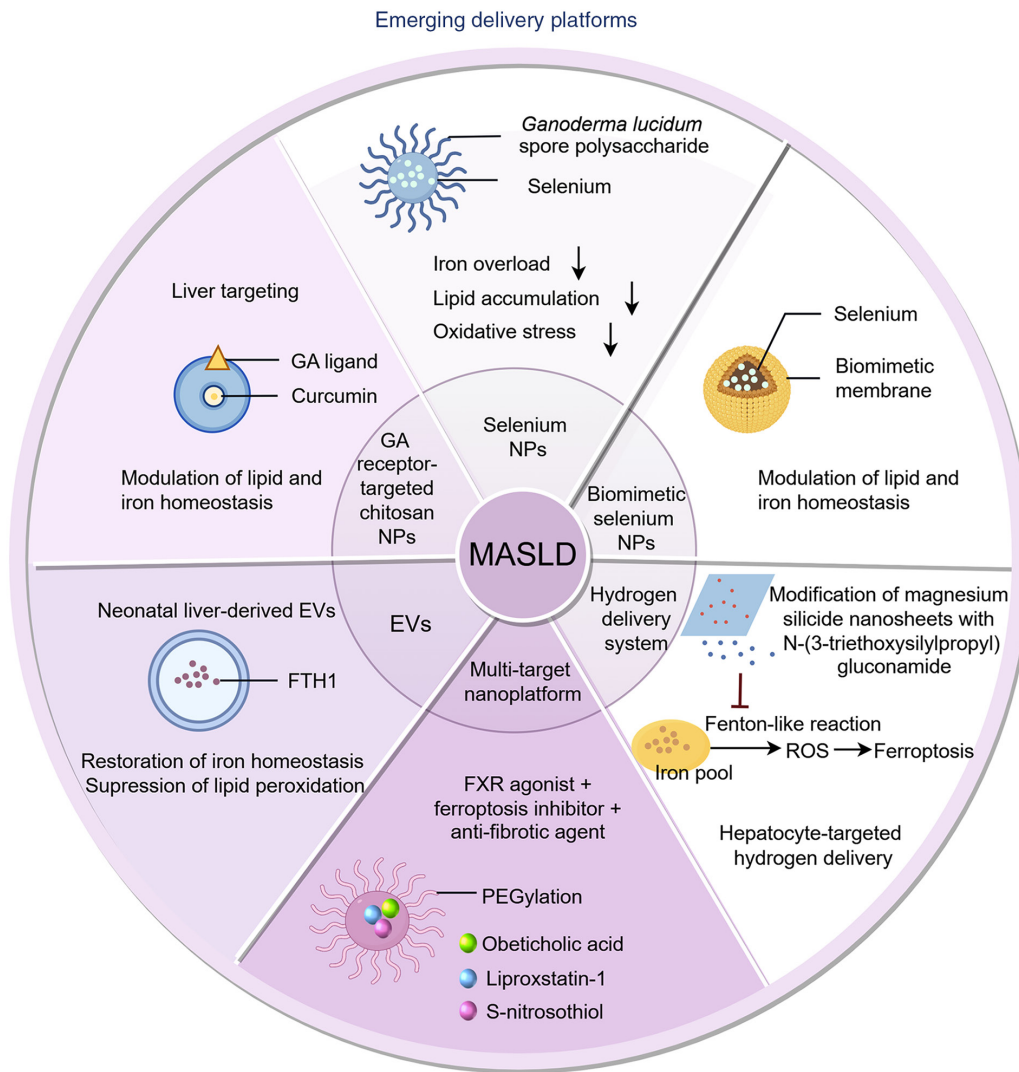


Figure 4. Delivery platforms for ferroptosis-targeted therapy in MASLD. Selenium NPs stabilized by *Ganoderma lucidum* spore polysaccharides and biomimetic selenium nanocomposites use natural antioxidant and redox properties of selenium to improve liver distribution. Chitosan NPs targeted through GA receptors facilitate liver-specific delivery. The multi-target nanoplatform delivers an FXR agonist, a ferroptosis inhibitor and an anti-fibrotic agent at the same time, allowing combination therapy. Hepatocyte-targeted hydrogen delivery removes free radicals and inhibits the Fenton reaction. FTH1-enriched EVs transfer FTH1 to hepatocytes and attenuate ferroptosis-associated changes. MASLD, metabolic dysfunction-associated steatotic liver disease; NP, nanoparticle; GA, glycyrrhetic acid; FXR, farnesoid X receptor; FTH, ferritin heavy chain; EV, extracellular vesicle; ROS, reactive oxygen species; PEG, polyethylene glycol. Created by Figdraw.

a metabolite produced by *Bacteroides uniformis*, is transported to the liver via the portal vein, where it inhibits the inositol-requiring enzyme 1 α /spliced X-box binding protein 1 signaling pathway. This inhibition alleviates liver fibrosis and suppresses ferroptosis-associated molecular changes (150). The aforementioned study provides novel insight into the links between gut microbiota, endoplasmic reticulum stress and hepatocyte ferroptosis. In addition, *Lactobacillus plantarum* 1-2-3 has beneficial effects on lipid metabolism and inflammation and protects against MASLD by modulating gut microbiota and metabolic pathways (151). Furthermore, acetate produced by *Akkermansia muciniphila* activates the hepatic AMPK/SIRT1/PPAR gamma coactivator 1 alpha (PGC-1 α) signaling pathway, thereby suppressing ferroptosis-associated signaling and ameliorating MASLD (152).

Obeticholic acid is promising therapeutic candidate in MASH (153). However, its antifibrotic efficacy is decreased by microbiota-induced lipid peroxidation. This inhibitory effect

largely originates from *Bacteroides*, which deconjugates tauro-conjugated bile acids, leading to aberrant production of chenodeoxycholic acid and subsequent accumulation of ROS in the liver (154). Collectively, these findings indicate that MASLD arises not only from hepatic dysfunction but also from gut and systemic metabolic perturbation, underscoring the importance of targeting the gut-liver axis.

6. Delivery platforms

Nanotechnology-based delivery systems have been developed to facilitate the delivery of multiple therapeutic agents and improve therapeutic outcomes. For example, selenium nanoparticles (NPs) stabilized with *Ganoderma lucidum* spore polysaccharides prevent MASLD in HepG2 cells, primarily through their antioxidant properties (155). Similarly, biomimetic selenium nanocomposites that modulate lipid and iron homeostasis alleviate MASH in choline-deficient, L-amino

acid-defined, high-fat diet induced MASH mice (156). These selenium-based systems exploit the natural redox properties of selenium and improve hepatic distribution. Targeted nanocarriers have also been developed. For example, glycyrrhetic acid receptor-targeted chitosan oligosaccharide NPs improve MASLD by inhibiting ferroptosis-associated signaling, although the exact anti-ferroptotic mechanism remains incompletely understood (157). In a more advanced approach, a single nanotherapeutic platform was designed to co-deliver an farnesoid X receptor agonist, a ferroptosis inhibitor and an anti-fibrotic agent for combination treatment of MASH, achieving greater efficacy than any single component alone (158). This multi-target strategy reflects the simultaneous involvement of metabolic, oxidative and fibrotic processes in MASLD and demonstrates how nanotechnology integrates these components into a single formulation.

Hepatocyte-targeted hydrogen delivery has also been developed to neutralize free radicals and inhibit the Fenton reaction, thereby preventing heme-induced lipid peroxidation (159). However, these strategies remain at the preclinical stage and represent a potential non-drug approach, although clinical feasibility remains to be established. In addition, a recent study reported the therapeutic potential of extracellular vesicles enriched with ferritin heavy chain 1 in mitigating ferroptosis-associated molecular changes and treating MASLD (160) (Fig. 4). This is consistent with a growing body of literature (161-163) highlighting the role of EVs in modulating cell processes and influencing disease outcomes.

7. Limitations

Targeting ferroptosis with iron chelators and inhibitors has promise in restoring redox and lipid homeostasis, suggesting a potential therapeutic strategy for MASLD (83). However, several barriers must be addressed before ferroptosis-targeted therapies can be translated into clinical practice.

A notable challenge is the incomplete understanding of the molecular mechanisms and regulatory networks governing ferroptosis in MASLD. Recent studies (15,83,164) have identified several pathways linking ferroptosis with MASLD progression, but how ferroptosis influences different disease stages remains poorly defined. Moreover, MASLD is not a single condition but a spectrum of liver disorders and ferroptosis may exert distinct effects at different stages. Treatment development therefore requires a stage-specific approach. In addition, systemic interactions between the liver, adipose tissue and gut microbiota further modulate ferroptosis susceptibility, offering opportunities for precision therapy.

Identifying reliable biomarkers of ferroptosis in MASLD is an active area of research. New biomarkers may enable early detection and monitoring of ferroptosis, but their clinical validation remains at an early stage and further studies are needed to establish their efficacy and reliability (83). Advanced tools such as imaging probes that detect ferroptosis within specific cell compartments would also substantially advance the field. For example, a viscosity-sensitive near-infrared fluorescent probe has been developed for sensitive visualization of lipid peroxidation in ferroptotic hepatocytes and dual-channel probes have been designed to detect multiple oxidative stress markers during ferroptosis (165,166). These platforms remain

preclinical, but may accelerate target validation and drug efficacy assessment in MASLD research.

The development of ferroptosis-targeting therapy shows promise, but clinical evaluation is key to ascertain safety and efficacy. Future therapeutic strategies should not aim merely to modulate ferroptosis systemically but should achieve cell-specific modulation with precise spatial and temporal control. This requires improved targeted delivery systems, dynamic biomarkers and a detailed map of communication pathways between diseased cells and their neighbors. For example, recent advances in nanotechnology have produced nanoagents that induce ferroptosis in tumor cells while sparing immune cells, providing a model for analogous strategies in MASLD, where immune cell preservation is key (167). In addition, the interactions between ferroptosis and necroptosis, pyroptosis and autophagy in MASLD remain largely unknown. Understanding of how these cell death pathways reinforce or compensate for one another is needed to predict the net effect of ferroptosis-targeting therapy.

Notably, the daidzein intervention on liver histopathology in patients with MASLD trial (trial no. NCT07623044), a Phase 2 study that is not yet recruiting, aims to evaluate the potential of short-term perioperative daidzein intervention in improving liver tissue health in patients with MASLD. The primary endpoint is the NAFLD Activity Score (168), with exploratory analyses examining GPX4, ACSL4 and intrahepatic CD8⁺ T cell infiltration. These secondary assessments aim to clarify whether daidzein exerts measurable effects on ferroptosis-associated pathways and the hepatic immune microenvironment. If successfully completed, this trial may provide human tissue-level evidence for ferroptosis modulation by a natural product in MASLD. Although preclinical findings are promising, the clinical use of ferroptosis-targeting strategies for MASLD is in its early stages. More clinical trials are needed to evaluate the therapeutic benefits of ferroptosis-targeting intervention for patients with MASLD, which is essential for translating basic findings into clinical practice.

8. Conclusion

In summary, although preclinical studies have demonstrated promising results, clinical evidence for ferroptosis-targeted therapy in MASLD remains limited, with most interventions still in early preclinical development. A deeper understanding of how ferroptosis interacts with other cell processes across different cell types, organs and disease stages is needed. Such work will help identify more precise molecular targets and support the development of cell-specific interventions that mitigate the harmful effects of ferroptosis while preserving its physiological roles. Clinical translation requires rigorous evaluation of efficacy and safety in well-designed trials, but this must follow adequate preclinical validation and should not be interpreted as imminent clinical readiness. These efforts may advance understanding of MASLD pathogenesis and inform the development of novel therapeutic strategies to improve patient outcomes.

Acknowledgements

Not applicable.

Funding

The present study was supported by Hubei Provincial Natural Science Foundation of China (grant no. 2026AFB252) and Research Foundation of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology (grant no. 2024B32).

Availability of data and materials

Not applicable.

Authors' contributions

XT wrote and revised the manuscript. ML revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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