Protective effect of traditional Chinese medicine on non-alcoholic fatty liver disease and liver cancer by targeting ferroptosis

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Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease with high incidence and is closely related to metabolic syndrome. If not controlled, it may eventually become hepatocellular carcinoma (HCC). Ferroptosis, a non-apoptotic form of programmed cell death (PCD), is closely related to NAFLD and HCC, and the mechanisms of action involved are more complex. Some studies have demonstrated that many drugs inhibit ferroptosis and protect liver steatosis or carcinogenesis. The role of Traditional Chinese Medicine (TCM), especially herbs or herbal extracts, has received increasing attention. However, there are relatively few review articles on the regulation of NAFLD by TCM through the ferroptosis pathway. Here, we summarize the TCM intervention mechanism and application affecting NAFLD/NAFLD-HCC via regulation of ferroptosis. This article focuses on the relationship between ferroptosis and NAFLD or NAFLD-HCC and the protective effect of TCM on both by targeting ferroptosis. It not only summarizes the mechanism of early prevention and treatment of NAFLD, but also provides reference ideas for the development of TCM for the treatment of metabolic diseases and liver diseases.

KEYWORDS
traditional Chinese medicine, active ingredient, ferroptosis, non-alcoholic fatty liver disease, protective effect

Introduction

Liver dysfunction leads to metabolic disorders and ultimately endangers personal health (1). For example, non-alcoholic fatty liver disease (NAFLD) is a manifestation of metabolic syndrome in the liver (2). Simple steatosis occurs when the intrahepatic fat content is > 5% due to of non-alcoholic or other secondary factors, and it can be further developed into non-alcoholic steatohepatitis (NASH). Nearly half of patients with NASH have the probability to develop liver fibrosis, cirrhosis, or even hepatocellular carcinoma.
and summarize the intervention mechanisms and applications of ferroptosis affecting the NAFLD disease. Review of the mechanism of action and clinical application of TCM that have been reported previously, providing ideas and information for the future development of herbs or herbal extracts for the prevention and treatment of NAFLD/NAFLD-HCC.

Ferroptosis and non-alcoholic fatty liver disease/non-alcoholic fatty liver disease-hepatocellular carcinoma

Ferroptosis

Ferroptosis is a non-apoptosis with a completely different morphology. Condensation of the cell membrane without affecting membrane integrity, blistering of the plasma membrane, increased density of the mitochondrial membrane, reduction or disappearance of the mitochondrial crest, and rupture of the mitochondrial outer membrane are typical characteristics of ferroptosis. It is often accompanied by complex networks of genes, proteins, and metabolisms, which means that it is associated with multiple mechanisms of occurrence. Iron metabolism imbalance, lipid peroxidation and the System Xc-/GSH/GPx4 axis imbalance are the “three hallmarks” of ferroptosis. Iron is well known to have two different valence states that can undergo redox reactions in vivo. The ferroptosis-sensitive cellular transferrin receptor 1 (TFR1) can transports Fe$^{2+}$ into cells for reduction to Fe$^{2+}$, which is stored in the intracellular unstable iron pool in the form of an iron storage protein complex consisting of a ferritin light chain polypeptide, and a ferritin heavy chain polypeptide in the presence of divalent metal transport protein 1 (DMT1). However, when excess free Fe$^{2+}$ is present in the cell, ferritin is recruited and solubilized by specific cargo receptor recognition, and the released excess Fe$^{2+}$ in turn increases the formation of hydroxyl radicals through the Fenton reaction, inducing reactive oxygen species (ROS) production and increased susceptibility to cellular ferroptosis.

Lipid peroxidation is an important factor driving ferroptosis. Polyunsaturated fatty acids (PUFAs) contain easily extractable diallyl hydrogen atoms, making it sensitive to lipid peroxidation and one of the essential elements for the occurrence of ferroptosis. Hydrogen of PUFAs is acquired by hydroxyl groups to form carbon-centered lipid atom groups (L-), and O$_2$ reacts rapidly with L- to produce lipid peroxidation atom groups (LOO-). Lipidomic results suggest that phosphatidylethanolamine (PE) containing arachidonic acid (AA) is the key membrane phospholipid for the occurrence of oxidation-driven ferroptosis. Acyl coenzyme A synthase long chain family member 4 (ACSL4) and Lys phosphatidylethanolamine acyltransferase 3 (LPCAT3) are involved in PE biosynthesis, activating PUFA and forming...
PUFA-PE. The loss of ACSL4 and LPCAT3 depletes substrates for lipid peroxidation and increases inhibition of ferroptosis. Eventually PUFA-PE further promotes ferric oxidation catalyzed by lipoxygenase (LOX) (32).

System Xc- is a heterodimeric cell surface amino acid reverse transmitter. Extracellular cystine will be transported into cell and reduced to cysteine for the synthesis of glutathione (GSH) (33). GSH is the major antioxidant in mammals and is a cofactor of GPx4. If the level of GSH is compromised by System Xc-, ROS will accumulate and ferroptosis will be initiated by GPx4 with reduced activity (34).

In addition to the above typical pathways that regulate cellular susceptibility to ferroptosis, several others also play a role. P53 is a tumor suppressor gene that inhibits System Xc- uptake by downregulating SLC7A11, affecting GPx4 activity and ultimately inducing ferroptosis (35). Nuclear factor erythroid-2-related factor-2 (Nrf2) is an important antioxidant regulator that promotes the HO-1, GSH, and GPx4 expression in the downstream, eliminates ROS accumulation in the liver, and reduces malondialdehyde (MDA) levels (36). Meanwhile, protein genes responsible for encoding GSH synthesis, such as SLC7A11, GCLC/GLCM, and GSS are all target genes of Nrf2 (37). The latest research has found that dihydroorotate dehydrogenase (DHODH) in mitochondria can regulate ferroptosis through a GSH-independent pathway, which provides a new idea for precise targeted regulation of ferroptosis (38). Therefore, the pathways regulating ferroptosis susceptibility are more abundant and are considered to have important implications in the pathogenesis, treatment or drug development, and specific studies may be more beneficial for its comprehensive understanding.

### Ferroptosis in non-alcoholic fatty liver disease

Metabolic changes and hepatocyte lip toxicity caused by the ectopic accumulation of free fatty acids (FFAs) in the liver are considered to be the principal causes of liver injury in patients with NAFLD (39). However, the mechanisms that drive simple steatosis to NASH, fibrosis and even cirrhosis and HCC are still not fully understood. Whereas the liver is an important organ for iron storage, and the content of iron and lipid ROS in the dysfunctional liver are significantly increased. Serum ferritin is usually showing a high level in patients with NAFLD, which is associated with intrahepatic iron accumulation (40). Insulin resistance is one of the key causative factors of NAFLD, and iron accumulation in the body can also interfere with the function of Islet β Cells, affecting insulin synthesis and secretion, and resulting in insulin resistance (41, 42). Various results suggest that iron metabolism and lipid peroxidation, as the main links in ferroptosis, are closely related to the pathogenesis of NAFLD.

Notably, as researches continue, it has been found that ferroptosis in the different stages of NAFLD may variable. Early results suggested that in addition to iron, levels of the
lipid peroxide MDA, 4-NHE, are simultaneously elevated in NAFLD patients (43). Vitamin E, the ferroptosis inhibitor, can reduce lipid peroxidation and improves liver injury (44). Subsequently, Tsurusaki et al. reported that ferroptosis in hepatocytes and intrahepatic macrophages may be the incentive for early simple steatosis and the progression from NAFLD toward to NASH; hepatocyte ferroptosis precedes apoptosis during the initial stages of NAFLD in model mice, leading to liver damage, immune cell infiltration, and inflammatory response (19). Contrastingly, ferroptosis inhibition results in reduced liver injury inflammatory and lipid peroxidation (19). This report provides the first clear insight into the relationship between ferroptosis and NAFLD, and contrasts the differences among hepatocyte ferroptosis, apoptosis and necrosis. Li et al. found that AA metabolism enhanced lipid ROS accumulation, and key regulatory factors of iron metabolism significantly were increased in MCD-induced NASH mice (21). However, these changes occurred after administration of a ferroptosis inhibitor, ferrostatin-1 (21). Increased Fe$^{2+}$ and AA may act jointly to promote lipid peroxidation and NASH. Excessive Fe$^{2+}$ impairs the function of pancreatic β cells and liver cells through oxidative stress and mitochondrial injury, leading to insulin resistance and affecting NAFLD development (41). Other studies have shown that ferroptosis may exacerbate the early inflammatory, oxidative stress, and cell damage in NASH (45). Further progression of NASH can lead to the development of liver fibrosis in patients. The key to the development of liver fibrosis is the activation of hepatic stellate cells (HSC). And HSCs are abundant in iron. Induce activation of HSCs promotes the accumulation of Fe$^{2+}$, elevates ROS levels, and leads to ferroptosis (46). In addition, HSCs contain the ferroptosis regulator P53, ELAV-like protein 1 (ELAV1) and zinc finger monoprotein 36 (ZFP), which have been reported to be effective targets for fibrosis prevention (47, 48). As previously mentioned, P53 inhibits SLC7A11 and reduces GPx4 activity, leading to ferroptosis in HSC. The p62-kelch-like ECH associated protein 1 (Keap1)-Nrf2 antioxidant signaling pathway is more frequently engaged in HCC, which is also involved in the regulation of ferroptosis. Inhibition or knockdown of Nrf2 enhanced erastin- or sorafenib-induced ferroptosis in HCC in vitro and in vivo (49). Non-coding RNAs (ncRNAs) are responsible for the regulation of tumorigenesis through various biological processes. Among them, microRNA (miRNA) regulates GSH, Fe levels, Nrf2 and ROS to regulate ferroptosis and inhibit cancer development (50, 51). LncRNAs mainly act as the regulatory factors of transcription factors in the nucleus or as miRNAs of sponges in the cytoplasm to regulate ferroptosis (52). In conclusion, ferroptosis is pivotal in the occurrence and progression of the NAFLD disease spectrum. However, unlike the early two stages, the promotion of cellular ferroptosis may be beneficial for liver fibrosis and HCC. This may also be a perspective to distinguish the severity of NAFLD.

### Intervention effects of herbs or herbal extracts in regulating ferroptosis on non-alcoholic fatty liver disease

Currently, there is no agreed standard or definitive effective drugs for the treatment of NAFLD. The commonly used chemotherapeutic drug sorafenib is resistant to treatment in patients with advanced HCC. Therefore, the search for more effective new drugs has become an urgent task. TCM occupies an equally important position as Western medicine in health management and disease treatment, and even numerous of clinical cases have proven to be superior in treatment of certain diseases (53–56). TCM is the natural treasure trove of compounds with a wide range of sources, a great deal of active ingredients, and the stability of structure (57). TCM intervention in ferroptosis has certain efficacy and value. For example, artemisinin and pipernine amide are believed to exert effective mechanisms of anti-cancer by interfering ferroptosis in HCC, pancreatic cancer and other tumor diseases (58, 59). Baicalin is also a natural inhibitor of ferroptosis, weakening lipid peroxidation and ROS production and protecting cells of acute lymphoblastic leukemia induced by RSL3 from ferroptosis (60). Herbs or compounds and derived compounds or extracts have a certain ameliorating effect on NAFLD based on antioxidants, lipid metabolism and intestinal microbiota regulation (61). Therefore, TCM can intervene with NAFLD (Figure 2) or NAFLD-HCC by regulating ferroptosis (Table 1 and Figure 3).

### Monomers

**Dehydroabietic acid**

Dehydroabietic acid (DAA) is a natural diterpenoid resin acid, which is primarily obtained by catalytic disproportionation of rosin abietic acid (62). It is stable in nature and has the properties of anti-tumor (63) and anti-inflammatory (64). DAA alleviates insulin resistance and weakens hepatic steatosis and lipid accumulation through activation of PPAR-γ and PPAR-α in high-fat diet (HFD) model mice, leading to reducing hepatic function (65). Further studies revealed that DAA was able to bind to Keap1 in the cytoplasm and increase the luciferase activity of Nrf2-antioxidant reactive element (ARE), promoting the expression of downstream antioxidant gene heme oxygenase-1 (HO-1), GSH, and GPx4 through the Keap1/Nrf2 pathway, while DAA treatment results in achieving attenuation of ROS and lipid peroxidation (36). Importantly, Nrf2 is a necessary transcription factor that regulates the cellular oxidative stress reaction and also controls Fe$^{2+}$, which is manifested as an inhibition of ferroptosis (27, 66). HO-1, an important source of intracellular iron, plays a key role in
FIGURE 2
Major molecules, genes, and metabolic networks for ferroptosis involved in NAFLD interfering by traditional Chinese medicine. Keap1, kelch like ECH associated protein 1; Nrf2-ARE, nuclear factor erythroid-2-related factor-2-antioxidant reactive element; TFR1, transferrin receptor 1; iREB2, iron-responsive element binding protein 2; FTH1, ferritin heavy chain; HO-1, heme oxygenase-1; GSH, glutathione; GPx4, GSH peroxidase 4; ROS, reactive oxygen species.

TABLE 1 Intervention effects of TCM in regulating ferroptosis on NAFLD.

| TCM          | Function                                                | Stage in NAFLD | References |
|--------------|---------------------------------------------------------|----------------|------------|
| DAA          | Activates Nrf2, leading to reducing lipid peroxidation  | Simple steatosis and NASH (36, 65, 67) |
| GB           | Activates Nrf2, leading to reducing lipid peroxidation  | Simple steatosis and NASH (70, 71) |
| Que          | Targets Mitochondrial ROS-Mediated Ferroptosis          | Simple steatosis and NASH (75–79) |
| EGCG         | Inhibits system Xc<sup>−</sup>, for preventing GSH consumption, GPx4 inactivation and lipid peroxidation | NASH (83–85) |
| DLT          | Increases Fe<sup>2+</sup> accumulation, promoting ubiquitination of the IREB2 protein and suppressing expression of FTH1 | Simple steatosis and NASH (90) |
| DHA          | Decreases the expression of GPx4, inducing HSC ferroptosis; Activates the anti-survival UPR and upregulates CHAC1 expression | Fibrosis, HCC (93–95) |
| ART          | Inhibits ubiquitination of IRP2, promoting its accumulation for HSC ferroptosis | Fibrosis (46) |
| Artesunate    | Activates HSC ferritinophagy/ferroptosis; Acts synergistically with sorafenib | Fibrosis, HCC (96, 97) |

ART, Artemether; CHAC1, Chac glutathione-specific γ-glutamylcyclo-transferase 1; DAA, Dehydroabietic acid; DHA, dihydroartemisinin; DLT, Danlou tablet; EGCG, Epigallocatechin Gallate; FTH1, ferritin heavy chain; GB, Ginkgolide B; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; Que, Quercetin; Nrf2, nuclear factor erythroid-2-related factor-2; ROS, reactive oxygen species; GSH, glutathione; GPx4, glutathione peroxidase; iREB2, iron-responsive element-binding protein 2; IRP2, iron regulatory protein; UPR, unfolded protein response.

ferroptosis induced by erastin (67). At the same time, DAA increased the expression of key genes of ferroptosis such as ferroptosis suppressor protein 1 (FSP1) in vivo and in vitro (36). Therefore, it is believed that DAA inhibits ferroptosis through activation of the Keap1/Nrf2 pathway and is a potentially effective means of treating NAFLD. One shortcoming, however, is that these studies did not compare DAA with ferroptosis inhibitors. If available, the credibility of DAA modulation of ferroptosis to improve NAFLD would be increased.

Ginkgolide B

Ginkgolide B (GB) belongs to terpene trilactones and is the main active ingredient in Ginkgo biloba leaf extract (68). Like DAA, the effect of anti-inflammatory function by GB is well known (69). Application of GB for treatment of HFD-induced obese mice reduced the body weight and triglyceride (TG) levels and improved steatosis in the liver (70). To verify whether the protective effect of GB on steatosis hepatocytes is related to ferroptosis and the underlying molecular mechanisms, Yang et al. conducted in vivo and in vitro experiments (71). Mice fed with HFD and HepG2 cells treated by palmitic acid (PA) oleic acid (OA) exhibited significant reduction in Fe<sup>2+</sup> concentrations and obvious increase in Fe<sup>3+</sup> concentrations, and both showed changes in combinations of biomarkers based on ferroptosis, such as the upregulation of TFR1, and the inhibition of Nrf2 expression (71). The reversal effect was
FIGURE 3
Summary of herbs or herbal extracts modulating the disease spectrum of NAFLD. NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma.

evident after GB administration, with a clear promotion in the expression of Nrf2, which facilitated iron metabolism and inhibited oxidative stress in the liver (71). And the effect of high concentrations of GB approximated that of the positive control drug atorvastatin, an ferroptosis inhibitor. TFR1, as an ferroptosis sensitive protein, also plays a crucial role in hepatic iron metabolism. It can be found that GB and DAA have similarities in the pathways related to the regulation of ferroptosis, both of which may mobilize downstream genes by influencing Nrf2 activity, and finally exert the role of anti-ferroptosis, while achieving a balance of iron metabolism and lipid peroxidation.

Quercetin

Quercetin (Que) is a polyhydroxy flavonoid widely distributed in fruits, vegetables, and the root, leave or fruit from medicinal plants. The antioxidant activity of Que is excellent, and the phenolic hydroxyl groups rich in its structure can inactivate free radicals by providing active hydrogen while being oxidized to a more stable form of free radicals themselves (72). In addition, Que is a natural iron chelator. Its B ring displays the catechol portion and multiple free hydroxyl groups that drive the reduction of Fe$^{3+}$ to Fe$^{2+}$ (73); and at pH 7.2, quercetin completely blocks the iron-promoted Fenton reaction at the micromolar level (74). This is an effective strategy to prevent excess iron-induced oxidative stress, which means that chelation with Fe$^{2+}$ is the key to the antioxidant activity of Que. And it is oxidative stress that plays a crucial role in the pathogenesis of NAFLD. Zhu et al. found that Que intake resulted in a 39% reduction in hepatic TG content and a 1.5-fold increase in VLDL in HFD-induced NAFLD rats (75). Yang et al. applied Que in NAFLD model in vivo and vitro and showed a significant decrease in serum transaminase levels, a recovery for liver superoxide dismutase, catalase and GSH levels, and a relieve in lipid accumulation (76). In a randomized, double-blind and controlled trial, 90 patients supplemented with Que twice daily for 12 weeks showed significantly higher erythrocyte levels but evidently lower mean erythrocyte volume and hemoglobin, as well as ferritin compared to controls (77). It was suggested that Que exhibits potent in animal models hepatoprotective effect and also beneficial for some NAFLD-related biomarkers in clinical patients. Recently, Jiang et al. found that lipid peroxidation, lipid accumulation and ferroptosis induced by HFD could be alleviated via Que supplementation in mice. Next, Que was found to markedly depress mitochondrial ROS production in FFA-treated L-02 cells, with similar effects to Fer-1, an ferroptosis inhibitor (78). Mitochondrial ROS is a unique property of ferroptosis that distinguishes it from other types of PCD, and chelation of Fe$^{2+}$ in the liver by Que reduced hepatocyte lipid peroxidation.
and ROS production. In addition, Que seems to have twofold properties. It was shown that for HepG2 hepatoma cells it was able to induce lysosomal activation mediated by transcription factor TFE3, promote ferroptosis, and eventually induce ferroptosis (79). However, the specific signaling pathway by which Que regulates mitochondrial ROS to improve NAFLD has not been elucidated, and this may be something that could be explored further.

**Epigallocatechin gallate**

Epigallocatechin Gallate (EGCG) is the main polyphenol catechin in green tea, with antioxidant and anti-inflammatory effects, and is also beneficial in metabolic syndrome and different types of liver injury (80, 81). These advantages rely on its unique structure. EGCG has three hydroxyl groups at carbons 3’, 4’, and 5’ of the B ring and an esterified gallate portion at carbon 3’ of the C ring, which contributes to its ability to scavenge free radicals and chelate transition metal ions (80). Data from multiple *in vitro* and *vivo* experiments showed that EGCG is helpful for improving NAFLD-related fibrosis and HCC (81). EGCG increases the activity of mitochondrial complexes, thus protecting lipid peroxidation to prevent hepatic steatosis (82). EGCG-treated rat liver showed a decrease. The MDA levels was significantly decrease, while GSH and SOD levels was clearly elevated in mice treated with EGCG (83), the antioxidant activity of the liver increased. In recent years, EGCG was found to be a novel ferroptosis inhibitor, which can prevent the depletion of GSH, inactivation of GPx4 and lipid peroxidation by chelating iron ion (84). Ning et al. investigated the effect of EGCG on NASH by intraperitoneal injection and gavage, and found that the iron accumulation in the liver of mice fed by both methods was significantly lower than that of the NASH group, and the long-chain fatty acid coenzyme ACSBG expression was increased, with a significant negative correlation to the iron accumulation in the liver of mice (84). Ethanol extracts of Danlou tablet (EEDT) can inhibit inflammation by downregulating the NF-κB single signal and promote the outflow of cholesterol and lipids by activating the PPARα/ABCA1 signaling pathway (90). Xin et al. established a model of NAFLD in HFD ApoE−/− mice to explore whether DLT mediates the occurrence and development of NAFLD through the ferroptosis pathway (91). After the DLT intervention, the Fe²⁺ levels in liver tissue of mice were significantly reduced, and the protein and mRNA expression levels of GPx4 and ferritin heavy chain (FTH1) were apparently elevated, and the cytoplasm was brownish yellow and dark in color (91). Moreover, the protein and mRNA expressions of iron-responsive element-binding protein 2 (IREB2) were reduced, and hepatocyte swelling was lightened, and the number of fat vacuoles was completely lessened (91). Unlike DAA and GB, IREB2 is a key indicator of cellular ferroptosis, and increased Fe²⁺ can promote ubiquitination of the IREB2 protein and suppress expression of FTH1. This is sufficient to proof that DLT targets ferroptosis to inhibit oxidative stress and inflammatory factor levels to achieve a protective effect on the liver of NAFLD model mice. The evidence on DLT still appears weak, so more verifications are necessary.

**Artemisinin compounds**

Artemisinin is the active ingredient of the dried stems and leaves of Artemisia annua, a member of the Asteraceae family, and belongs to the sesquiterpenoids. The derivatives of it include dihydroartemisinin (DHA), artemether (ART), artesunate and so on. In addition to anti-malaria, artemisinin compounds also have various pharmacological effects such as anti-inflammatory and anti-fibrotic (92). Zhang et al. found that DHA triggered ferroptosis to eliminate the activation of HSC, which characterized by iron overload, GSH depletion, lipid ROS accumulation, and peroxidation, whereas Fer-1 and Lip-1 inhibited the DHA effect (93). Shen et al. reported similar results, at the same time, they discovered that DHA attenuates liver fibrosis by activating autophagy to trigger ferroptosis in HSC (94). In addition, DHA induced ferroptosis as an antitumor agent in primary liver cancer (PLC) by activating the anti-survival unfolded protein response (UPR) and upregulating CHAC1 expression, which was significantly attenuated by Fer-1 and DFO application after iron loading (95). These reveal a potential mechanism by which DHA ameliorates liver fibrosis or PLC, and moreover suggest that ferroptosis is a favorable method to eliminate activated HSC or PLC cells. ART was detected to promote the accumulation of iron regulatory protein (IRP2) by inhibiting its ubiquitination, thus inducing an increase in iron content, generating a large amount of ROS and leading to the onset of ferroptosis of HSCs (46). Kong et al. demonstrated...
that artesunate obviously evoked ferroptosis of activated HSC in fibrotic liver, as characterized by decreased cell viability, accumulated iron, elevated lipid peroxidation, and diminished antioxidant capacity. In contrast, the inhibition of DFO almost abolished the antifibrotic effect induced by artesunate (96). Artesunate is a clinically well-tolerated compound that acts synergistically with sorafenib to induce ferroptosis in the HCC cell lines Huh7, SNU-449, and SNU-182 (97). Thus, artesinin compounds have prominent effects as ferroptosis inducers to hinder HSC activation in the liver fibrosis stage of NAFLD, resulting in antifibrosis. In addition, all the above results imply a possible interaction between autophagy and ferroptosis from another perspective, which deserves to be explored in depth.

Conclusion and perspectives

With the increasing incidence and the wide spread of complications, NAFLD has become one of the most concerned chronic liver diseases. The unclear pathogenesis is a major obstacle to the treatment of NAFLD, and at present, the main focus is to protect liver with pharmacological, especially TCM. The core steps of ferroptosis are reflected in the development of the NAFLD disease spectrum, and the manifestation at different stages may vary according to the current pathological features, which also opens a new approach for the study of the hepatic protective mechanism of TCM. Although studies on the improvement of NAFLD by intervention of ferroptosis in herbs or herbal extracts are not well reported yet, these suggest their strong potential to be used as natural ferroptosis inhibitors. Compared to classical ones, they have the advantage of being widely available, less expensive, more stable, and fewer side effects. In addition to the above mentioned, there are many studies on the protective effect of liver by herbs or herbal extracts through the means of anti-lipid peroxidation. Hesperidin has been shown in in vitro and in vitro experiments to upregulate antioxidant levels by activating the PI3K/AKT-Nrf2 pathway and alleviate liver steatosis by inhibiting NF-κB-mediated inflammation (98). Bicycl, extracts of Wuweizi, has a wide range of pharmacological effects that attenuate tetracycline-induced hepatic steatosis, and hepatic lipid accumulation and physalide steatosis are ameliorated (99). They are all potential regulators for ferroptosis, and whether the mechanisms involved in liver protection are related to the ferroptosis pathway that ultimately led to the regulation of NAFLD should be further explored in works. For HCC, several therapies or drugs have been tried in the clinic, but no breakthroughs have been achieved, and even some approved drugs later failed to inhibit tumor growth due to the emergence of drug resistance mechanisms. Ferroptosis is considered to be the most promising tumor growth inhibitor that can affect the development and progression of HCC by regulating intracellular iron levels and ROS (100). This provides new therapeutic options for patients with HCC. The research prospect of TCM targeting ferroptosis is very promising, and although there are some undeniably limitations and difficulties involved, the meaning for the prevention and treatment of NAFLD and NAFLD-HCC is great. For example, ferroptosis is involved in the occurrence and development of NAFLD and can serve as an independent predictor of early alterations in NAFLD, as well as a potentially important target for prevention and treatment in clinical practice. However, the disadvantage is that most of the current research focuses on animal models, and there is still less evidence to prove the mechanism of ferroptosis from the molecular level or in clinical patients. Whether ferroptosis or other forms of PCD can be clearly distinguished during the disease for targeted prevention and treatment is also deserves further exploration. In addition, Studies on the regulation of ferroptosis by herbs or herbal extracts at different stages of NAFLD development to achieve intervention remains inadequate, and the related mechanisms need to be further explored as well.

Author contributions

QW and ZC designed the study, searched the literature, and drafted the manuscript. YD and YT made the figures. YC edited the manuscript and supervised the work. All authors approved the final manuscript.

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Conflict of interest

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mediated pathways.

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Dehydroabietic acid suppresses inflammatory response via suppression of Src-, Syk-, and Tak1-
inhibitors.

Mol Divers.

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