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Progress on the mechanism of food polyphenols in the prevention of liver fibrosis

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Abstract Liver fibrosis is the formation of extracellular matrix deposits due to excessive repair of chronic liver damage. Liver fibrosis is a necessary stage in the progression of cirrhosis, and timely intervention reverses the pathogenesis. Liver fibrosis is a dynamic and highly integrated molecular, cellular and organisational process. Currently, no specific drug is used to treat liver fibrosis, and liver transplantation is the main clinical treatment for cirrhosis. Chemical drugs are often designed to target individual genes or proteins, with kinds of side effects. Food polyphenols, which are available and safe, have unique advantages and great potential in the treatment with the liver fibrosis. This review summarizes the pathogenesis of liver fibrosis and provides examples of food polyphenols' anti-liver fibrosis mechanisms that have been identified in recent studies, and provides some sights for the development of anti-liver fibrosis drugs.

Keywords: food polyphenols; liver fibrosis; mechanism

1 Introduction

According to some statistics, the prevalence of severe and advanced liver fibrosis in the China is 8.34% and 2.85%, respectively [1]. Associated with the progression of liver disease, fibrosis is a key pathological processes in the prognosis of liver disease and hepatocellular carcinoma (HCC). Liver fibrosis were caused by viral hepatitis (mainly hepatitis C virus (HCV) and hepatitis B virus (HBV)), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cholestasis, parasitic diseases (mainly schistosomiasis), and autoimmune disease [2-5]. The mechanisms are poorly understood. Research has demonstrated that liver fibrosis can be reversed [6]. Fibrosis is a key factor for liver disease outcome and risk of hepatocellular carcinoma (HCC). However, the reversal process is slow and delaying treatment, which can make it more challenging to recover as the disease advances to later stages. But liver fibrosis complications only become apparent in the later stages. Antifibrotic therapies to slow the progression of liver disease are inadequate. Currently, most clinical treatments for liver injury are based on liver transplantation and there are no recognized effective chemical or biological agents. The prevention and treatment of liver fibrosis are increasingly important. Therefore, the search for effective anti-liver fibrosis drugs and active ingredients is of great significance.

Polyphenols are a class of plant compounds with numerous health benefits. They are water-soluble antioxidants that have been reported to promote health and have been suggested for the treatment of metabolic disorders [7]. Polyphenols are compounds

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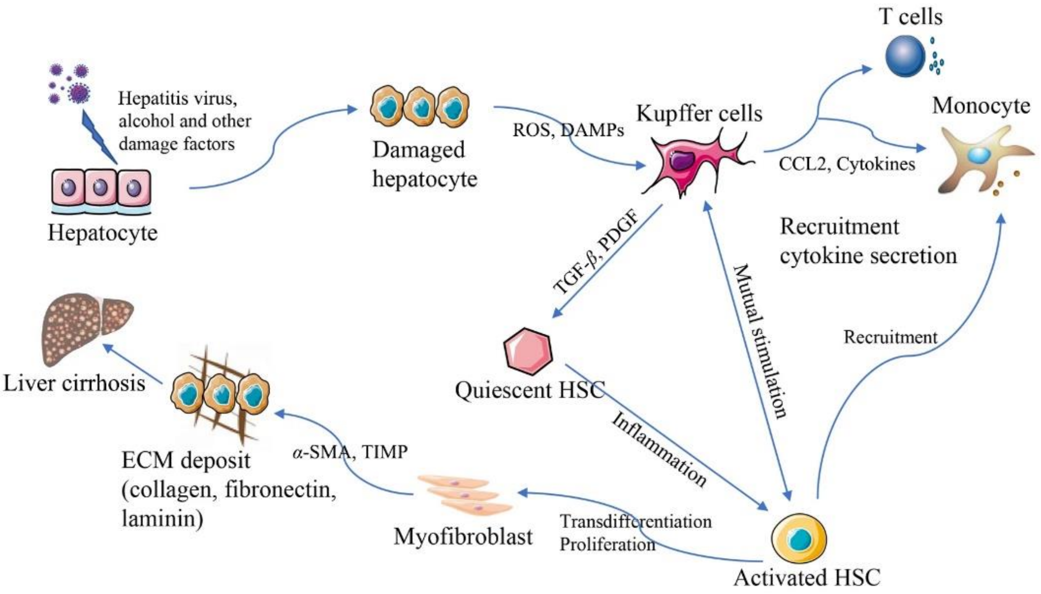
that contain multiple phenolic hydroxyl groups and are reported in a wide variety of foods, including fruits, vegetables, grains, tea, coffee and wine. Polyphenols can be classified into several categories, including phenolic acids, flavonoids (such as isoflavones, neoflavones, flavanones and flavanols), polyphenol amides, and non-flavonoids (such as resveratrol, ellagic acid and curcumin) [8]. Its unique structure of polycyclic aromatic hydrocarbons gives it the ability to reduce oxidative free radicals and exert antioxidant effects. Polyphenols have been shown to inhibit liver fibrosis. This paper aims to review recent polyphenol compounds for the treatment of liver fibrosis and make recommendations for the development of drugs against liver fibrosis.

2 Pathogenesis of liver fibrosis

Liver inflammation is associated with hepatocellular damage and lobular inflammation, and can progress to fibrosis, cirrhosis and hepatocellular carcinoma [9]. Fibrosis is a healing response to trauma, where the damaged area is encapsulated by extracellular matrix or scarring, caused by the accumulation of extracellular matrix (ECM) proteins that replace damaged normal tissue. As noted by Yao, et al. [10] in mid-2022, liver fibrosis can be caused by multiple factors that contribute to chronic liver disease (Fig. 1). This paper classifies and describes the pathogenesis as either toxin liver injury or cholestatic liver injury.



Note: Liver fibrosis is initiated by hepatic injury and the subsequent imbalance of ECM synthesis and degradation mediated by activated HSCs. Cirrhosis is the most advanced stage of liver fibrosis.

Fig. 1 Pathogenesis of liver cirrhosis [10]

2.1 Toxin-induced liver injury

Toxic liver injury can be caused by alcohol, chemicals, drugs, dietary supplements or metabolite abnormalities. Chronic viral infections, alcohol consumption, and metabolic syndrome are the primary causes of hepatotoxicity-induced liver fibrosis.

2.1.1 Chronic viral infections

In the past two decades, chronic hepatitis B and C viral infections have been the leading cause of liver fibrosis. The mechanism by which viral hepatitis causes liver fibrosis is primarily the inflammatory response caused by virus-induced hepatocyte injury, death, and apoptosis [5] in which HBV infection is a major cause. However, the underlying mechanisms for the development of HBV-induced fibrosis remains elusive, and efficacious therapies for this disease are still lacking. In the progression of HBV or HCV-associated CLD, the prevailing pro-fibrotic mechanism is chronic activation of wound healing. ROS and oxidative stress also contribute significantly. Evidence indicates that the immune response drives the activation and development of fibrosis following initial liver injury. The T-helper lymphocyte subtype 17 (Th17)/interleukin-17 (IL-17) axis has been identified as a key factor in the immunopathology and prognosis of patients with CVH, along with other immune dysregulations [11]. In the liver, Th17 cells produce the cytokine IL-17, and receptors for IL-17 are expressed on hepatocytes, hepatic sinusoidal endothelial cells, hepatic stellate cells (HSCs) and Kupffer cells (KCs). The functional roles of IL-17 in hepatic tissues are mainly in the activation or stimulation of HSCs and KCs, as well as cholangiocytes [12-15]. The incidence of liver disease caused by viral infections has markedly decreased due to the sustained advancement of antiviral drugs.

2.1.2 Alcohol consumption

The prevalence of non-viral liver diseases, including ALD, NAFLD, and DILI (drug-induced liver injury), has been increasing in recent years. The liver is the primary site for alcohol metabolism. Prolonged ingestion of substantial quantities of ethanol can lead to metabolic disorders, which in turn result in the accumulation of acetaldehyde in liver tissue and subsequent liver cell death. This process oxidases ethanol to acetaldehyde, producing reactive oxygen species (ROS) and initiating oxidative stress and inflammation [16]. The histopathological features of non-alcoholic fatty liver disease (NAFLD) include the accumulation of lipid droplets in hepatocytes, balloon-like degeneration of hepatocytes, lobular inflammation, and perisinusoidal fibrosis or cirrhosis [17].

2.1.3 Metabolic syndrome

NAFLD has become one of the most prevalent chronic liver diseases. Metabolic syndrome is a pathological condition characterized by the abnormal assembly of multiple metabolic components, which in turn affects the pathophysiological processes of the liver, particularly in relation to lipid metabolism. In 1998, Day CP et al. proposed the theory of “two hits” at the international level. The “first hit” is the accumulation of liver fat caused by obesity and insulin resistance, while the “second hit” is oxidative stress [18]. Changes in the gut microbiota also contribute to the latter [19]. Subsequent research has demonstrated that the pathogenesis of non-alcoholic fatty liver disease (NAFLD) is more complex than the previously proposed “two-hits” theory. The current “multiple-hits” theory suggests that the “first hit” is still hepatic lipid deposition and insulin resistance. This is influenced by a number of factors, including genetic susceptibility, inflammatory pathways, and hepatocyte metabolism. However, these components are not exhaustive [20]. Steatosis is caused by the excessive accumulation of triglycerides, fatty acids, or cholesterol in steatotic hepatocytes. This accumulation is associated with the activation of the transcription factors PPARγ, SERBP1, SERBP2, and the expression of caspase-2. Dysregulated release of lipocalin, leptin, or resistin leads to insulin resistance and increased inflammation [21, 22]. We now show that caspase-2, whose expression is ER-stress inducible and elevated in human and mouse NASH, controls the buildup of cholesterol and triglycerides by activating sterol regulatory element-binding proteins (SREBP). The second effect is related to the generation of reactive oxygen species (ROS), LPS derived from the gut, and the subsequent release of pro-inflammatory (TNF, IL-6, IL-1β, IL-17, and leptin) and pro-fibrotic (TGF-β) cytokines, resulting in HSC activation [23]. ROS and oxidative stress production are associated with almost all CLD diseases. They can cause hepatocyte injury and death and inhibit parenchymal cell proliferation, while also directly and indirectly maintaining fibre formation.

2.2 Cholestatic liver injury

Impaired bile flow caused by bile duct obstruction or genetic defects can result in the accumulation of bile acids (BA) in the liver and body circulation, resulting in cholestatic liver disease. This condition can cause progressive liver fibrosis and, ultimately, liver failure [24]. The farnesol X receptor is expressed at high levels in the liver and intestine of mammals and has been identified as an important pharmacological target for the treatment of intrahepatic cholestasis, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [25]. FXR regulates the activity of CYP7A1, which is the rate-limiting enzyme in bile acid synthesis. Chen Ming, et al. demonstrated that activation of FXR up-regulates CYP7A1 gene expression and reduces α-naphthylisothiocyanate (ANIT)-induced liver injury in rats. This confirms that these modulations help to reduce bile acid synthesis, increase bile acid metabolism, promote bile acid blood flux, and ultimately reduce intrahepatic cholestasis [26]. Biliary atresia is a developmental disease that affects newborns. It is caused by a congenital occlusion of the bile duct, which leads to cholestasis, hepatocyte apoptosis, and rapid progression to biliary fibrosis. Most patients with biliary atresia require liver transplantation [23].

3 Classical dietary polyphenols with anti-liver fibrosis properties and their mechanisms

Polyphenolic compounds, which were as natural antioxidants, play an important role in the antifibrotic process. They effectively inhibit the pathological process of fibrosis through a variety of mechanisms, including modulation of cellular signal transduction pathways, inhibition of inflammatory factor expression and oxidative stress.

3.1 Silymarin

Silymarin is both a liver-protecting herb and a high-quality cooking oil ingredient. In the United States, silymarin is one of the best-selling herbal dietary supplements. Silymarin is a polyphenolic compound containing flavonoid lignans and flavonoids extracted from the dried fruit of MT. The main flavonoid lignans are silybin, isosilybin, silybinin, and silydianin [27, 28]. Silymarin acts as a natural antioxidant by a mechanism that may prevent the formation of free radicals by inhibiting enzymes that produce reactive oxygen species (ROS) [27, 29]. As mentioned in Table 1, some researchers have reported that silymarin significantly reduces superoxide dismutase (SOD), reduced glutathione (GSH), glutathione-S-transferase (GST), and glutathione reductase (GSR), thereby inhibiting hepatic oxidative stress [30]. Yang reported that silymarin significantly reduced up-regulated CYP2E1 mRNA and protein expression in the livers of mice with acetaminophen (APAP)-induced acute liver injury, and also significantly attenuated APAP overdose-induced hepatic pathology in mice [31]. Silymarin oil (SMO) is a by-product of silymarin production, and SMO was effective in modulating dyslipidaemia and attenuating hepatic fat accumulation in HFD mice, which may be based on the inhibition of oxidative stress and modulation of lipid metabolism-related factors. In addition, oral administration of the oil was observed to improve hepatic fatty acid synthesis and fatty acid oxidation by decreasing the mRNA levels of fatty acid synthase (FAS), hepatic X-receptor α and sterol regulatory element binding protein 1c (SREBP-1c) [32]. In addition to oxidative stress, studies have shown that silymarin can exhibit anti-inflammatory effects by inhibiting the release of cytokines [33-35]. Some researchers have found the effect of the crud extract of Silybum marianum, with high polyphenolic content, on experimental nonalcoholic steatohepatitis (NASH). Ou, et al. reported that silymarin attenuated hepatic steatosis and fibrosis in MCD diet-induced NASH mice, possibly by inhibiting the NF-κB inflammatory pathway and suppressing oxidative stress through upregulation of Nrf2 [34]. Zhao reported that silymarin reduced the extent of liver injury and decreased inflammatory cytokines in serum and liver, and its mechanism of action may be related to activation of the Nrf2/HO-1 pathway and inhibition of the NF-κB/NLRP3 pathway [36].

Table 1 Example of silymarin against liver fibrosis (*In vivo*)

Polyphenol type	Animal type	Model	Disease type	Mechanism	Ref.
Silymarin	Rat	N-nitrosodiethylamine (NDEA)	Hepatocarcinoma	Inhibitting oxidative stress	[30]
	SD rat	Acetaminophen	Acute liver injury	Reducing the activity and expression of CYP2E1	[31]
Silybum marianum oil	ICR mice	High fat diet	Obesity	Improving lipid metabolism while attenuating lipid accumulation, oxidative stress, and inflammation	[32]
The crud extract of silybum marianum	N-Mary rat	Methionine and choline deficient diet	Steatohepatitis	Inhibition of oxidative stress, TNF and JNK signaling	[33]
Silybin	C57BL/6 mice	Methionine and choline deficient diet	Steatohepatitis	Activation of the Nrf2 pathway and inhibition of the NF-κB signaling pathway	[34]
	C57BL/6 mice	High fat diet	Obesity	Inhibition of NLRP3 inflammasome assembly occurs via the NAD+/SIRT2 pathway	[35]
Silymarin	KM mice	D-Gal/LPS	Multiple-organ damage	Activation of the Nrf2/HO-1 signaling pathway and inhibition of the NF-κB/NLRP3 signaling pathway	[36]

3.2 Chlorogenic acid

Chlorogenic acid (CGA) is an important bioactive dietary polyphenol that is a major component of coffee. Chlorogenic acids (CGAs) represent the entire group of hydroxycinnamates with quinic acid, including caffeic acid, ferulic acid, dicaffeoylquinic acid and coumaroylquinic acid. Previous studies have shown that approximately 33% of CGA can be absorbed through the human small intestine [37, 38]. Reduction in the risk of a variety of diseases following CGA consumption has been mentioned in recent basic and clinical research studies. This systematic review discusses *in vivo* animal and human studies of the physiological and biochemical effects of chlorogenic acids (CGAs). CGA has been reported to have the active effects of lowering blood pressure, blood sugar and cholesterol, weight loss, anticancer, hepatoprotection, intestinal barrier protection, as well as a placebo effect [37]. Studies have shown that clindamycin (TM) is an endoplasmic reticulum stressor that induces endoplasmic reticulum stress in hepatocytes and leads to hepatic steatosis [39]. Some of the mechanisms of chlorogenic acid in the treatment of liver injury are shown in Table 2. Moslehi used TM to induce endoplasmic reticulum stress in mice and reported that 20 mg/kg CGA reduced mRNA levels of Grp78, Ire-1 and Perk. In addition, TM-induced liver injury was prevented by altering lipid accumulation in steatosis and markers of adipogenesis (SREBP-1c, PPAR-α, and Fas), and inhibited inflammation (NF-κB, TNF-α, and IL-6) and markers of apoptosis (caspase-3, p53, Bax, and Bcl-2) in hepatic tissues of endoplasmic reticulum-stressed mice [40]. Ji, et al. [41] reported that CGA reduced the AP-induced increase in the number of hepatic apoptotic cells and also inhibited AP-induced cleavage activation of caspase-3 and reduced oxidative stress enzyme activity. Furthermore, CGA eliminated AP-induced activation of phosphorylation of ERK1/2, c-JunN-terminal kinase (JNK), p38 kinase and upstream molecular signaling. Shi, et al. [42] reported that CGA reduced the degree of liver fibrosis in CCL_4-induced rats and decreased the expression of TIMP-1 and CYP2E1. In addition, increasing the expression of nuclear Nrf2 and Nrf2-regulated antioxidant factors (HO-1, GCLC, and NQO1). *In vitro* studies reported that CG reduced PDGF, ROS production, phosphorylation of p38 and ERK1/2, proliferation of HSCs, and expression of pro-fibrotic genes. The results suggest that CGA prevents CTC-induced liver fibrosis, by inhibiting hepatic and hepatic stellate cells from oxidative stress to prevent CTC-induced liver fibrosis. Yang, et al. [43] also reported that CGA may attenuate liver fibrosis through the miR-21-regulated TGFβ1/Smad7 signaling pathway.

Table 2 Example of chlorogenic acid against liver fibrosis (*In vivo*)

Animal type	Model	Disease type	Mechanism	Ref.
C57BL/6 mice	Tunicamycin	Hepatic steatosis	Reduction of NF-κB and caspase-3 to ameliorate hepatic apoptosis and inflammation	[40]
ICR mice	Acetaminophen	Drug-induced liver injury	Regulating liver MAPK signaling cascade	[41]
SD rat	CCl_4	Liver fibrosis	Nrf2 pathway; PDGF-induced NOX/ROS/MAPK signaling pathway in HSCs	[42]
SD rat	CCl_4	Liver fibrosis	Blocking the miR-21-Regulated TGF-β1/Smad7 Signaling Pathway	[43]

3.3 Tea polyphenols

Polyphenols are the main active compounds in tea, among which catechins are the main polyphenols, and epigallocatechin-3-gallate (EGCG), is the most researched active compound in the study of green tea catechins [44]. EGCG improves body weight and glucose and lipid metabolism by activating AMPK [45]. Some of the mechanisms of tea polyphenols in the treatment of liver injury are shown in Table 3. GTPs reduced inflammatory cell infiltration and attenuated collagen and fat deposition in di (2-ethylhexyl) phthalate (DEHP)-induced liver injury, identifying the mmu-miR-141-3p/Zcchc24 (mRNA)/Zcchc24 (protein) regulatory axis, which plays a crucial role in the therapeutic effects of GTPs on DEHP-induced liver injury [46]. EGCG inhibits macrophage inflammatory vesicle activation (reduced IL-1β and IL-18 secretion, NLRP3, caspase-1 p20, IL-1β-p17, and cysteine asparaginase-1 activity) by the mechanism that EGCG inhibits macrophage inflammatory vesicles by down-regulating extracellular HMGB1 levels [5]. In present investigation, we investigated the effect and mechanism of green tea polyphenol epigallocatechin-3-gallate (EGCG. It was reported that EGCG inhibited TGF-β1-stimulated Smad2/3 phosphorylation by suppressing the inhibitory effect of the PI3K/Akt/Smad pathway on liver fibrosis gene expression [47]. Further studies verified that tea polyphenols also inhibited the phosphorylation of Smad1. Not only did it improve liver function markers, but it also attenuated oxidative stress (e.g., decreased MDA, increased SOD activity, etc.) and showed a significant ability to restore glutathione activity. In addition, the expression of MMP2 and MMP9 mRNA was downregulated [48]. Al-Basher showed that polyphenols in green tea extract reduced iron accumulation, serum hepcidin and ferritin in iron-overloaded rats, thereby inhibiting oxidative stress induced by iron overload. In addition, it reduced liver serum cytochrome C and inhibited hepatocyte apoptosis [49].

Table 3 Example of tea polyphenol against liver fibrosis (*In vivo*)

Polyphenol type	Animal type	Model	Disease type	Mechanism	Ref.
Green tea polyphenols	C57BL/6J mice	Di (2-ethylhexyl) phthalate	Non-alcoholic fatty liver	Regulate immune cell infiltration; Improvement of liver function and lipid changes	[46]
EGCG	C57BL/6-Tg mice	HBV	Viral liver fibrosis	Suppressed macrophage inflammasome through downregulating the level of extracellular HMGB1	[5]
	SD rat	Bile ductligated	Cholestatic liver fibrosis	Inhibiting the PI3K/Akt/Smad pathway	[47]
ECG, EGC, and EGCG	SD rat	CCl_4	Liver fibrosis	Inhibiting ERK and Smad1/2 phosphorylation	[48]
Green tea extract	SD rat	Iron over-loaded	Liver fibrosis	Inhibition of hepatic iron accumulation ameliorates hepatotoxicity, apoptosis and oxidative stress	[49]

3.4 Resveratrol

Resveratrol (RESV) is a polyphenol compound with a diphenylethylene structure that can be extracted from a wide range of natural plants, mainly from tiger nuts, grapes, wine and peanuts, etc. It is a phytoantitoxin that is produced by many plants in response to irritation [50-53]. Some of the mechanisms of resveratrol in the treatment of liver injury are shown in Table 4. RESV can inhibit hepatic inflammation by affecting neutrophils during hepatic ischemia-reperfusion injury model mice (HIRI) by the underlying mechanism of inhibition of survival, cell cycle, migration and chemotaxis, oxidative stress, cytokine secretion, and autocrine endothelin 1 via inhibition of the ERK signaling pathway [54]. RESV was reported to be effective in preventing hepatic TG accumulation and ameliorating insulin resistance through activation of AMPK in a variety of liver injury models, and is thought to be involved in SIRT1 [55, 59]. The breast cancer resistance protein (BCRP) is responsible for eliminating drugs and exogenous substances from organs such as the liver. Studies have shown an up-regulated expression of BCRP in liver disease, and a reduction in BCRP expression has been observed in a model of AP-induced hepatic injury treated with RESV. It was reported that this treatment restored the mitochondrial structure and liver ultrastructure, ultimately promoting liver regeneration in mice trans-isomer [56, 60, 61]. RESV was reported to regulate the SIRT1-p53 signaling pathway to promote cell cycle and liver regeneration and prevent hepatotoxicity by inhibiting CYP-mediated APAP bioactivation, and reduced phosphorylation of JNK2 was observed in AP-treated mice, possibly inhibiting liver injury through the JNK pathway [57]. Zhang, et al. demonstrated that RESV regulates autophagy and apoptosis through activation of the SIRT1 and JNK signaling pathways, thereby inhibiting HSC activation. However, autophagy and apoptosis may act independently on the SIRT1 and JNK pathways, or they may interact with each other, which needs to be further investigated [62]. RESV increases SIGIRR transcription and blocks the TLR/NF-κB signaling pathway to negatively regulate the expression of hepatic inflammatory factors, a potential pathway to prevent the onset and progression of NASH [58]. Piceatannol is a natural analog and a metabolite of resveratrol present in grapes and red wine. The anti-fibrotic mechanism of piceatannol was reported to be associated with the regulation of the transforming growth factor-β (TGF-β)/Smad signaling pathway [63].

Table 4 Example of resveratrol against liver fibrosis (*In vivo*)

Animal type	Model	Disease type	Mechanism	Ref.
C57BL/6 mice	Hepatic ischemia-reperfusion injury	Hepatic ischemia-reperfusion injury	Inhibiting the ERK/c-Fos signaling pathway	[54]
KKAy mice, C57BL/6 mice	Genetic obesity model KKAy mice	Obesity and diabetes	Up-regulation of SIRT1 and AMPK	[55]
C57BL/6 mice	Acetaminophen	Drug-induced liver injury	Reduces BCRP expression and stimulates hepatocyte proliferation	[56]
C57BL/6 mice	Acetaminophen	Drug-induced liver injury	Regulation of SIRT1/p53 signaling pathway, inhibition of CYP-mediated APAP bioactivation	[57]
C57BL/6 mice	Methionine and choline deficient diet	Steatohepatitis	Blocking TLR/NF-κB activation and apoptosis	[58]

3.5 Curcumin

Curcumin belongs to the class of diketones and is the main active ingredient in turmeric. Turmeric is a common spice used in the preparation of curry in India and other Asian countries, in addition, its use as a natural coloring agent, flavoring and medicine has spread to many countries. Recent studies have reported curcumin to have antioxidant, anti-inflammatory, anticancer and anti-angiogenic effects. It also has significant effects on other metabolic disorders, such as polycystic ovary syndrome, metabolic syndrome, dysglycaemia and non-alcoholic fatty liver disease [64-66]. Some mechanisms of curcumin in the treatment of liver injury are shown in Table 5. Curcumin inhibits oxidative stress by up-regulating PPAR-α expression and increases AMPK and decreases PI3K/AKT/mTOR and TGF-β/Smad expression, which regulate upstream signaling of autophagy, thereby enhancing autophagy and thus inhibiting the EMT process in hepatocytes [67]. Curcumin was reported to reduce the expression of HIF-1α and p-ERK by inhibiting the ERK pathway, and *in vitro* experiments revealed a significant inhibitory effect of curcumin when exposed to HSC proliferation [68]. The chemokine CXCL12 interacts with its receptor CXCR4 to form coupled molecular pairs, a very important signaling pathway *in vivo*. CXCL12/CXCR4 promotes HSC migration and chemotaxis in liver fibrosis, and researchers have reported that curcumin can effectively inhibit the CXCL12/CXCR4 axis, thus preventing HSC activation and migration to exert anti-liver fibrosis effects [69]. Curcumin regulates the activity of the alcohol metabolizing enzyme CYP2E1 enzyme as well as regulates lipid metabolism by increasing activated protein kinase (AMPK) expression. Curcumin inhibits chronic ethanol-induced hepatic oxidative stress and lipid peroxidation by inducing Nrf2 activation through the ERK/p38-MAPK pathway and upregulating the expression of detoxification genes, such as NQO1, HO-1, and GCLC [70, 71].

Table 5 Example of curcumin against liver fibrosis (*In vivo*)

Animal type	Model	Disease type	Mechanism	Ref.
SD rat	CCl_4	Liver fibrosis	Upregulation of PPAR-α expression increases autophagy, thereby inhibiting the EMT process in hepatocytes	[67]
SD rat	CCl_4	Liver fibrosis	Decreasing HIF-1α and ERK1/2 expression	[68]
SD rat	CCl_4	Liver fibrosis	Inhibiting the CXCL12/CXCR4 biological axis	[69]
Balb/c mice	Ethanol-exposed Balb/c mice	Chronic ethanol-induced liver injury	Induction of Nrf2 activation through the ERK/p38-MAPK pathway	[70]

3.6 Ellagic acid

Ellagic acid (EA) is a polyphenol found in fruits, nuts and herbs not only in its free form, but largely in the form of hydrolysable tannins called ellagitannins [72, 73]. Some of the mechanisms of ellagic acid in the treatment of liver injury are shown in Table 6. It was reported that EA reduced catalase activity in a CCL_4 induced liver injury in rat, via reduction of Bcl-2 and NF-κB expression and increasing of caspase-3 and Nrf-2 expression in the treatment group, thereby reducing the rate of liver injury in rats [74]. It has been verified that EA reduces NF-κB levels and increases Nrf-2 levels, in addition to inhibiting hepatic steatosis by activating AMPK [75]. EA exerts its antifibrotic activity by inducing iron apoptotic cell death in activated HSCs, which is accompanied by redox-active iron accumulation, lipid peroxidation and GSH depletion, and overexpression of HSC-specific VAMP2 impairs EA-induced HSC ferroptosis [76]. Kim, et al. [77] reported that EA reduced levels of TNF-α and IL-1β and decreased levels of oxidative stress marker proteins such as nitric oxide synthase iNOS, CYP2E1 and 3-NT, with slight but significant increases in apoptosis marker proteins p-JNK and Bax. Some researchers have evaluated the *in vitro* free radical scavenging and iron chelation potential of EA, which reveals the hepatoprotective activity of EA against iron overload-induced toxicity by scavenging free radicals, inhibiting excessive ROS production, normalizing liver injury parameters and up-regulating caspase-3, PARP expression [79]. But excess iron accumulation in the biological system accelerates oxidative stress, cellular toxicity, tissue injury and organ fibrosis, which ultimately leads to the generation of chronic liver diseases including cancer. EA has a therapeutic effect on thioacetamide-induced liver fibrosis in rats by down-regulating the expression of MMP9 and MMP2 by a mechanism that may be due to the interaction of the active sites of MMP9 and MMP2 with zinc, which leads to their inactivation, thereby alleviating the fibrosis [78].

Table 6 Example of ellagic acid against liver fibrosis (*In vivo*)

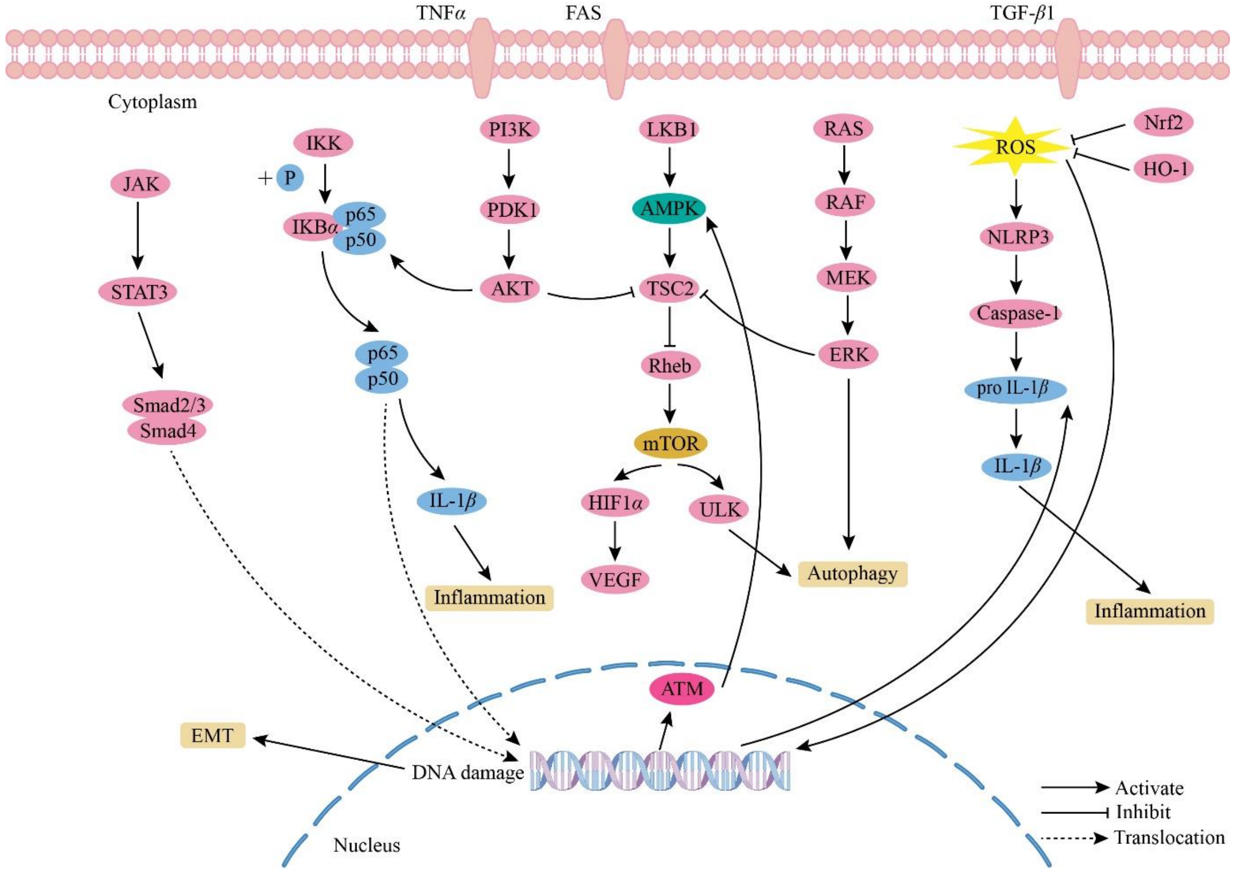
Animal type	Model	Disease type	Mechanism	Ref.
Wistar rat	CCl_4	Liver fibrosis	Inhibition of the NF-κB pathway; promotion of the Nrf-2 homofugal pathway	[74]
Wistar rat	Streptozotocin	Non-alcoholic fatty liver disease	Activation of AMPK inhibits hepatic steatosis	[75]
C57BL/6 mice	CCl_4	Liver fibrosis	Inducing FPN-dependent ferroptosis of HSCs by disrupting the formation of SNARE complexes	[76]
C57BL/6J mice	Ethanol	Alcoholic liver disease	Reduced levels of TNF-α and IL-1β and reduced levels of oxidative stress marker proteins	[77]
Rat	Thioacetamide	Liver fibrosis	Downregulation of MMP9 and MMP2 expression	[78]

3.7 Others

In adipocytes, mangiferin exerts a protective effect against ethanol-induced liver injury by inhibiting inflammation-stimulated lipolysis in adipose tissue. This is achieved through the activation of AMPK/ULK1/TBK1 signaling pathway, which subsequently inhibits NF-κB activation [80]. Mangiferin has been reported to attenuate CCl_4-induced liver injury and inflammatory response, regulate bile acid metabolism and pro-fibrotic gene expression, and may inhibit liver fibrosis through the NF-κB pathway [81]. Heat shock protein 27 (HSP27) may play a pivotal role in hepatocyte epithelial-to-mesenchymal transition (EMT) and liver fibrosis through the activation of the JAK2/STAT3 signaling pathway and the TGF-β1/Smad pathway. Mangiferin has been demonstrated to achieve anti-liver fibrosis by blocking the pathway through inhibition of HSP27 expression [82]. Proanthocyanidins exert anti-liver fibrosis effects by restoring redox balance, inhibiting inflammatory cytokines, normalising apoptosis regulatory proteins (Bax, caspase-3, and caspase-9, with increased Bcl-2) [83]. The polyphenols from Aronia melanocarpa have been demonstrated to treat lipopolysaccharide (LPS)-induced liver disease in rats. This is achieved by inhibiting LPS-induced hepatocyte apoptosis and modulating intestinal flora [84]. The mechanism by which this is achieved through gut microbiota modulation remains unclear. Here, a rich-polyphenol extract of A. melanocarpa (AMPs). The mechanism by which Aronia melanocarpa attenuates alcohol-induced liver injury may be related to the regulation of Nrf2 signaling through PI3K/Akt activity [85]. In the initial stages of NASH, bergamot polyphenolic formulation has the potential to reverse the lipid-induced hepatic redox imbalance in mice by inhibiting the ROS/JNK/p38-MAPK pathway [86]. Grape seed extract attenuates MTX-mediated liver injury by modulating the TLR4/NF-κB and Nrf2/HO-1 axis [87].

4 Conclusion

Treatment of liver fibrosis focuses on anti-inflammatory and multimodal approaches targeting hepatic stellate cells to inhibit collagen fiber formation and promote collagen degradation. HSC activation can be effectively suppressed by inhibiting the TGF-β1/Smad2 pathway. Polyphenols affect the process of liver fibrosis through inflammation, autophagy, apoptosis and iron death pathways (Fig. 2). Initial studies have focused on inhibition of the NF-κB inflammatory pathway. Currently, there are studies on the regulation of cellular autophagy by modulating ERK and apoptosis by modulating JNK. Recently, studies have begun to investigate polyphenols as anti-liver fibrosis via the iron death pathway. In addition, a large body of literature suggests that polyphenols may regress liver fibrosis by affecting the gut flora and thereby regressing liver fibrosis. Therefore, an in-depth study of the interactions and benefits of different polyphenols, as well as their possible synergistic effects in therapy, will provide useful insights for the development of more effective anti-liver fibrosis drugs in the future.



Note: Multiple signaling pathways are involved in the process of liver fibrosis and act synergistically. It can affect liver fibrosis through inflammatory and autophagic pathways.

Fig. 2 Mechanistic pathways of liver fibrosis

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