Review

Research progress on the anti-hepatic fibrosis action and mechanism of natural products

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ARTICLE INFO

ABSTRACT

Hepatic fibrosis is the most common pathological feature of most chronic liver diseases, and its continuous deterioration gradually develops into liver cirrhosis and eventually leads to liver cancer. At present, there are many kinds of drugs used to treat liver fibrosis. However, Western drugs tend to only target single genes/proteins and induce many adverse reactions. Most of the mechanisms and active ingredients of traditional Chinese medicine (TCM) are not clear, and there is a lack of unified diagnosis and treatment standards. Natural products, which are characterized by structural diversity, low toxicity, and origination from a wide range of sources, have unique advantages and great potential in anti-liver fibrosis. This article summarizes the work done over the previous decade, on the active ingredients in natural products that are reported to have anti-hepatic fibrosis effects. The effective anti-hepatic fibrosis ingredients identified can be generally divided into flavonoids, saponins, polysaccharides and alkaloids. Mechanisms of anti-liver fibrosis include inhibition of liver inflammation, anti-lipid peroxidation injury, inhibition of the activation and proliferation of hepatic stellate cells (HSCs), modulation of the synthesis and secretion of pro-fibrosis factors, and regulation of the synthesis and degradation of the extracellular matrix (ECM). This review provides suggestions for the development of anti-hepatic fibrosis drugs.

1. Introduction

Hepatic fibrosis is a reversible pathophysiological process and is a compensatory reaction in the process of liver damage and tissue repair after inflammation caused by various chronic pathogenic factors, hepatic fibrosis is also a necessary stage in the progression of chronic liver disease to cirrhosis, which is characterized by excessive and abnormal deposition of extracellular matrix (ECM) components in the liver [1–3].

According to the latest data, the number of deaths from liver cancer and cirrhosis is increasing worldwide, and the mortality rate is high because liver cancer is usually not diagnosed until its terminal stage. In addition, China is a highly endemic area of viral hepatitis, with about 120 million chronic infections of hepatitis B (HBV) [4,5]. Therefore, it is particularly important to treat hepatic fibrosis before it evolves into cirrhosis or even liver cancer [6,7]. Moreover, the importance of the prevention and treatment of hepatic fibrosis has gradually increased over the years, so it is of great significance to seek effective anti-hepatic fibrosis drugs and active ingredients [8,9].

Natural products generally refer to endogenous chemical components in living organisms, such as plants, animals and microorganisms [10]. Natural products have always been an important source of drug research and development due to their diverse chemical structures and extensive biological activities. Pharmaceutical preparations from natural products account for 30% of clinical drugs worldwide, and 65% of the global population uses natural products [10]. In recent years, more and more studies and data have shown that hepatic fibrosis and even early cirrhosis can be reversed if treated in time [11,12]. However, the treatment efficacy of traditional Western medicine is not ideal because it often results in a series of adverse reactions. Additionally, due to the complex underlying pathophysiology of hepatic fibrosis, there is a lack of specific effective Western-medicine drugs in clinical practice [13,14]. A large number of active components have been found in natural products, and these components exhibit structural diversity and few adverse reactions [10,15]. Therefore, it is of great significance to discover anti-hepatic fibrosis drugs from natural products that may cure a variety of diseases [16–18]. Many natural products are efficacious in the prevention and treatment of hepatic fibrosis, but there have been few detailed reports. In this paper, the

progress in research from the last 10 years on natural products for treating liver fibrosis is reviewed, and suggestions are provided for the development of anti-hepatic fibrosis drugs.

2. The anti-hepatic fibrosis action of natural products

The search for and discovery of anti-hepatic fibrosis drugs or lead compounds from natural products has recently become a popular area of research [6,10]. In recent years, a large number of domestic and foreign researchers have conducted much research on natural products and have made noteworthy progress [9,13,19]. Some natural products classified as alkaloids, polysaccharides, flavonoids, polypeptides, terpenes and polyphenols have been found to have anti-hepatic fibrosis activity [10,20,21]. These anti-hepatic fibrosis effects of natural products will be summarized according to these classifications.

2.1. Alkaloids

As an important natural product, alkaloids are numerous in application and complex in structure. Most alkaloids have significant physiological activity, and the anti-hepatic fibrosis effect of some alkaloids has been gradually discovered [22,23]. Nowadays, with increasingly serious liver diseases, the anti-hepatic fibrosis effect of alkaloids has been widely studied [24–26]. In recent years, alkaloids with significant anti-hepatic fibrosis effects have been found and are shown in Table 1 and Fig. 1.

2.2. Polysaccharides

Polysaccharides are a type of natural polymer and are among the most abundant in nature, exhibiting characteristics of having multiple components and multiple targets [36–38]. In recent years, research on polysaccharides has become a prominent focus in the field of medicine, as shown in Table 2.

2.3. Flavonoids

Flavonoids are a group of compounds that each have a 2-phenyl chromogenic ketone structure and are widely distributed in nature. They are found in fruits, vegetables and TCM [46–48]. Flavonoids have been a primary focus in drug research and development for their

diverse physiological activity and low toxicity. Various therapeutic hepatic fibrosis herbs used in the clinic contain flavonoids [49–51]. A large number of studies in recent years have also confirmed that many flavonoids extracted from natural substances have significant inhibiting effects on hepatic fibrosis, as shown in Table 3, Figs. 2 and 3.

2.4. Terpenoids

Terpenoids are olefin compounds that each have a molecular formula that is an integer multiple of isoprene. Some natural terpenes are widely found in nature and exhibit anti-hepatic fibrosis activity [71–73]. Many TCM natural products such as glycyrrhizin, radix *bupleuri*, *Panax notoginseng* and *Panax ginseng* contain terpenoids, as shown in Table 4 and Fig. 4.

2.5. Phenols

Phenolic compounds are a group of compounds that each contains polyhydroxyl phenols, which have antioxidant, anti-tumor, and antiviral properties, as well as many other biological activities [77–79]. Recent studies have found that some natural polyphenols have anti-hepatic fibrosis effects, as shown in Table 5 and Fig. 4.

3. Mechanisms of natural products in treating hepatic fibrosis

3.1. Protection of liver cells and reduction of liver damage

Liver injury is the initiator of hepatic fibrosis [19,20]. Long-term liver injury can lead to fatty liver cirrhosis, hepatic fibrosis and even liver cancer. Therefore, protecting liver cells and alleviating liver injury is an important mechanism to ameliorate hepatic fibrosis [21].

3.1.1. Inhibition of liver inflammation

Inflammation is a potential starting point of hepatic fibrosis [22,32]. Wai et al. [22] found that *Acanthus ilicifolius* alkaloid A and its acetylated derivatives have beneficial effects against liver fibrosis, and the mechanisms may be related to the inhibition of inflammatory responses (Fig. 1). Zhao et al. [32] found that oxymatrine could effectively attenuate CCl_4-induced hepatic fibrosis, and this effect may be due to modulation of TLR4-dependent inflammation and TGF-β1 signaling pathways (Fig. 1). Zhang et al. [38] found that *Dicliptera chinensis*

Table 1
Alkaloids with anti-hepatic fibrosis function.

Category/active ingredients	Source	Model	Mechanism	References
Monor alkaloid				
Acanthus ilicifolius alkaloid A	*Acanthus iliciifolius*	A	Inhibition of inflammatory response	[22]
Berberine	*Coptis chinensis*	B	Inhibiting the AMPK pathway	[23]
Caffeine	*Coffea*	C	Dampening the cAMP/PKA/CREB pathway	[24]
Capsaicin	*Capsicum annuum L.*	D	Inhibiting the TGF-β1/Smad pathway via PPAR-γ activation	[25]
Conophylline	*Catharanthus roseus*	E	Suppresses HSC and induces apoptosis	[26]
Evodiamine	*Tetradium ruticarpum*	A	Downregulation of relative expression of TGF-β1, p-Smad 2/3, and α-SMA	[27]
Ligustrazine	*Ligusticum chuanxiong*	A	Interrupting Nrf2/β-catenin pathway	[28]
Matrine	*Sophora flavescens*	D	Reduce TGF-β1 expression and enhance the activity of HGF	[29]
Melatonin	*Juglans regia*	A	Inhibiting TGF-β1/Smad Signaling Pathway	[30]
Neferine	*Nelumbo nucifera Gaertn*	A	Decreased expression of TGF-β1 in the liver	[31]
Oxymatrine	*Sophora flavescens*	A	Modulation of TLR4-dependent inflammatory and TGF-β1 signaling inhibited NFkappaB transcriptional activity, TGF-β1 and α-SMA expression	[32]
Tetrandrine	*Stephania tetrandra*	D	Inhibited TGF-β1-induced α-SMA secretion and collagen deposition	[33]
Total alkaloids				
Corydalis saxicola alkaloids	*Corydalis saxicola*	A	MEDIATED the regulation of multiple metabolic pathways	[34]
Mistletoe Alkaloids	*Viscum coloratum*	A	Inhibition of HSC activation via TGF-β/Smad interference	[35]

A. CCl_4-induced hepatic fibrosis.
B. bile duct ligation-(BDL-) induced liver fibrosis.
C. alcohol-induced liver fibrosis.
D. DMN-induced hepatic fibrosis.
E. thioacetamide-(TAA-) induced hepatic fibrosis.

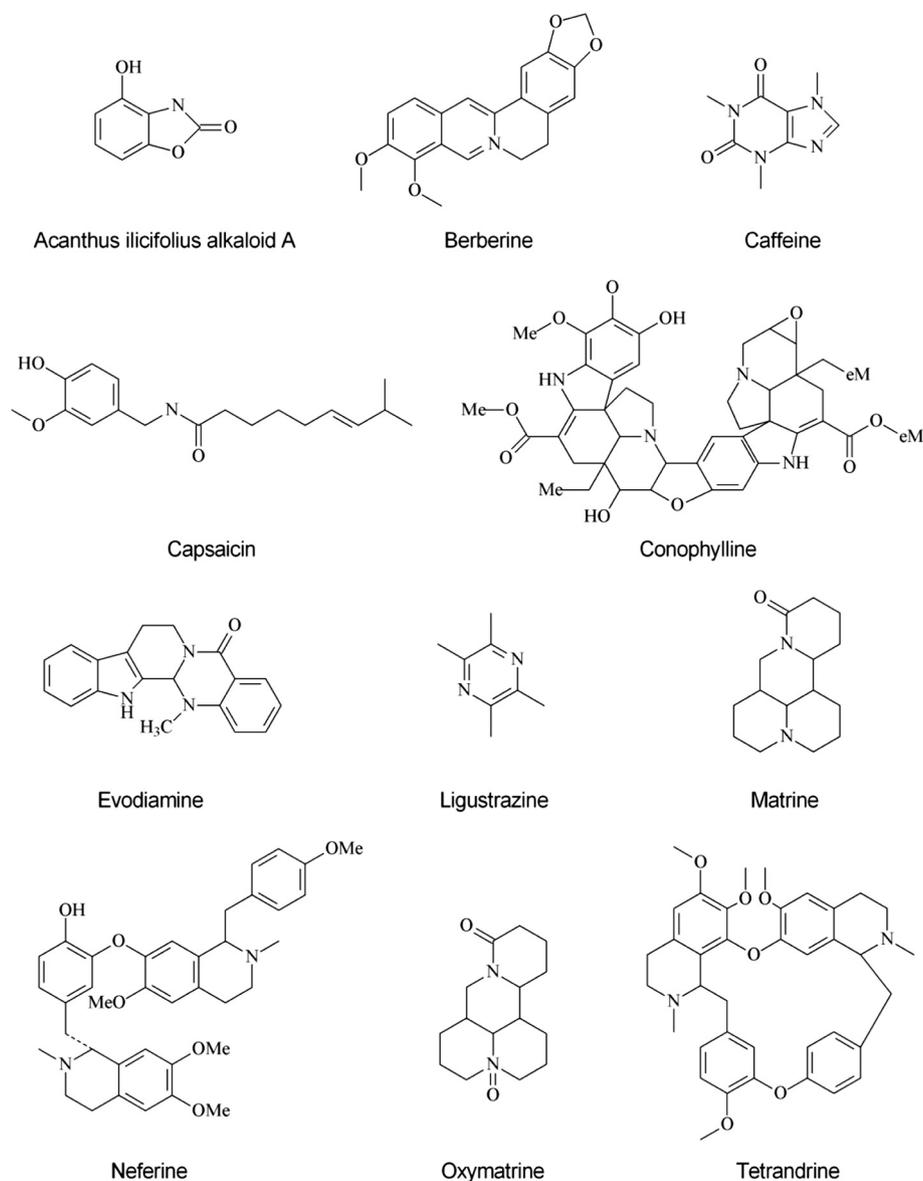**Fig. 1.** Structural formula of alkaloids with anti-hepatic fibrosis effects from natural products.

Table 2
Polysaccharides with anti-hepatic fibrosis function.

Category/active ingredients	Source	Model	Mechanism	References
Polysaccharides				
Astragalus polysaccharides	*Astragalus membranaceus*	A	Hepatoprotective effect	[36]
Cordyceps polysaccharides	*Cordyceps sinensis*	A	Inhibiting HSC activation, TGF-β1/Smads signaling pathway, as well as MMP2, MMP9 activity and TIMP2 expression.	[37]
Dicliptera chinensis polysaccharides	*Dicliptera chinensis*	B	Regulating functionally serous enzymes, improving metabolic function and inhibiting inflammatory reaction in liver tissue.	[38,39]
Fucoidan	*Phaeophyta*	A/C	Downregulation of TGF-β1/Smads pathways.	[40]
Garlic polysaccharide	*Allium sativum*	D	Inhibiting intestinal microflora dysbiosis	[41]
Lycium barbarum polysaccharides	*Lycium barbarum*	A	Inhibiting the TLRs/NF-kB signaling pathway expression.	[42]
Phellinus lineus polysaccharides	*Phellinus lineus*	E	Regulation of oxidative stress pathways, heat shock pathways, and metabolic pathways for amino acids and nucleic acids.	[43]
Polysaccharide from Amusium Pleuronectes	*Amusium Pleuronectes*	A	Hepatoprotective effects	[44]

A. CCl$_4$-induced hepatic fibrosis.
B. DMN-induced hepatic fibrosis.
C. BDL-induced liver fibrosis.
D. alcohol-induced liver fibrosis.
E. TAA induced hepatic fibrosis.

Table 3
Flavonoids with anti-hepatic fibrosis function.

Category/active ingredients	Source	Model	Mechanism	References
Flavonoid monomer				
Apigenin	*Apium graveolens*	A	Apigenin dose-dependently reduced collagen I	[45]
Baicalin	*Scutellaria baicalensis*	B	Promote differentiation of bone marrow-derived MSCs into hepatocytes in vitro	[46]
Breviscapine	*Erigeron breviscapus*	B	Inhibiting inflammatory apoptotic response and ROS generation	[47]
Chrysin	*Oroxylum indicum*	B	Inhibition of HSCs activation and proliferation through TGF-β1/Smad pathway	[48]
Diosmin	*Bitter orange*	C	Boosting PPAR-γ expression and hampering miR-17-5p activated canonical Wnt/β-catenin signaling	[49]
Hesperetin	*Citrus reticulata*	D	Inhibiting TGF-β1/Smad pathway-mediated extracellular matrix progression and apoptosis	[50]
Hesperidin	*Citrus reticulata*	B	Inhibit the activation and proliferation of HSC through targeting the Wnt/β-catenin signaling pathway	[51]
Hyperoside	*Hypericum perforatum L.*	A	Induced cells apoptosis	[52]
Icaritin	*Herba Epimedium*	B/D	Induce cell death in activated HSCs through mitochondria-mediated apoptosis	[53]
Morin	*Cudrania cochinchinensis*	B	Inducing the expression of Nrf2 and its downstream antioxidant factors	[54]
Myricetin	*Myrica rubra*	B	Inhibits the activation of HSCs	[55]
Naringenin	*Amacardium occidentale*		Blocking TGFβ-Smad3 and JNK-Smad3 pathways	[56]
Oroxylin A	*Oroxylum indicum*	B	Activation of autophagy	[57]
Proanthocyanidin	*Grape*	B	Suppressed lipid peroxidation	[58]
Puerarin	*Puerariae lobata*	E	Attenuation of inflammation response and amelioration of metabolic function.	[59]
Puerarin	*Sophora flavescens Ait*	B	The regulation of NF-κB/IκBα, p38 MAPK, and Bcl-2/Bax signaling	[60]
Silibinin	*Silybum marianum*	B	Hepatoprotective, antioxidant, free radical scavenging, membrane stabilizing and anti-fibrotic activity	[61]
Wogonoside	*Scutellaria baicalensis*	B	Significant protective effects against liver fibrosis	[62]
Total flavonoids				
Flavanones from *Sedum sarmentosum*	*Sedum sarmentosum*	B	Inhibition of TGF-β/TβR/Smad pathway in turn inhibiting epithelial mesenchymal transition	[63]
Flavonoid compounds extracted from Iris species	*Iris tectorum Maxim*	G	Hepatoprotective effects	[64]
Hemerocallis citrine baroni flavonoids	*Hemerocallis citrina baroni*	B	Decreasing the oxidative stress	[65]
Luteolin	*Dracocephalum integrifolium*	B/D/F	Prevents the progression of liver fibrosis through multiple mechanisms	[66]
Silymarin	*Silybum marianum*	B	Decrease in fibrotic parameters such as CTGF	[67]
Total flavonoids from *Litsea coreana*	*Litsea coreana* var. *sinensis*	B	Ameliorate liver injury and protect rats from liver fibrosis	[68]
Total flavonoids of *Bidens pilosa*	*Bidens pilosa*	B	Inhibiting the induction of NF-kappaB on HSC activation and the expression of TGF-β1	[69]
Yulangsan flavone	*Millettia pulchra*	B	Attenuating free radicals, inhibiting lipid peroxidation and accelerating extracellular matrix degradation	[70]

A. HSC model.
B. CCl₄-induced hepatic fibrosis.
C. radiation-induced liver fibrosis.
D. BDL-induced liver fibrosis.
E. TAA-induced hepatic fibrosis.
F. DMN-induced hepatic fibrosis.
G. Schistosoma Japonicum-(S. jap-) induced hepatic fibrosis.

polysaccharides effectively antagonize the activity of dimethylnitrosamine (DMN) -caused hepatotoxicity in hepatic fibrosis rats, for which the anti-fibrotic mechanisms were associated with regulating functionally critical enzymes, improving metabolic function and inhibiting inflammatory reactions in liver tissue. Baicalin inhibits the expression of TNF-α protein and has a protective effect on rats with hepatic fibrosis induced by CCl₄ [46] (Fig. 2). Liu et al. [47] found that CCl₄-induced oxidative stress was blocked by breviscapine through improving anti-oxidants and impeding mitogen-activated protein kinase pathways. Additionally, their study highlighted that breviscapine exhibited liver-protective effects against acute hepatic injury induced by CCl₄ via suppressing inflammation and apoptosis (Fig. 2). Li et al. [59] found that puerarin successfully reversed hepatotoxicity in CCl₄-induced hepatic fibrosis rats via regulation of serum enzymes and attenuation of the TNF-α/NF-κB pathway for anti-inflammatory responses, as well as by improving metabolic function in liver tissue (Fig. 3). Lai et al. [71] found that artesunate could alleviate hepatic fibrosis induced by multiple pathogenic factors and inflammation through the inhibition of the LPS/TLR4/NF-κB signaling pathway in rats, suggesting that artesunate may be a potential candidate for the therapy of hepatic fibrosis (Fig. 4).

3.1.2. Anti-lipid peroxidation injury

In the study of resistance to hepatic fibrosis, antioxidant and free radical scavenging are commonly elucidated mechanisms [36,54]. Yan et al. [36] found that lignans from Fructus *Schisandrae chinensis* and *astragalus* polysaccharides display hepatoprotective and antioxidant properties and act in a synergistic manner in CCl₄-induced liver injury in rats. Sang et al. [54] found that morin could play a protective role by inducing the expression of Nrf2 and its downstream antioxidant factors (HO-1 and NQO1), as well as by reducing the expression of α-SMA, collagen I, and collagen III in CCl₄-induced liver fibrosis rats (Fig. 3). HernándezAquino et al. [56] found that naringenin prevents CCl₄-induced liver inflammation, necrosis and fibrosis due to its antioxidant capacity as a free radical inhibitor and by inhibiting the NF-κB, TGF-β-Smad3 and JNK-Smad3 pathways (Fig. 3). Shen et al. [65] found that *Hemerocallis citrina baroni* flavonoids may inhibit CCl₄-induced liver injury by decreasing oxidative stress. Yuan et al. [69] found that the total flavonoids of *Bidens bipinnata* L. could ameliorate liver injury and protect rats from CCl₄-induced liver fibrosis by suppressing oxidative stress. This process may be related to inhibiting the induction of NF-κB on HSC activation and the expression of TGF-β1. Guo et al. [70] found that *Yulangsan* flavone has a certain curative effect on rats with CCl₄-induced liver fibrosis, and its mechanism may include attenuation of free radicals, inhibition of lipid peroxidation and acceleration of ECM
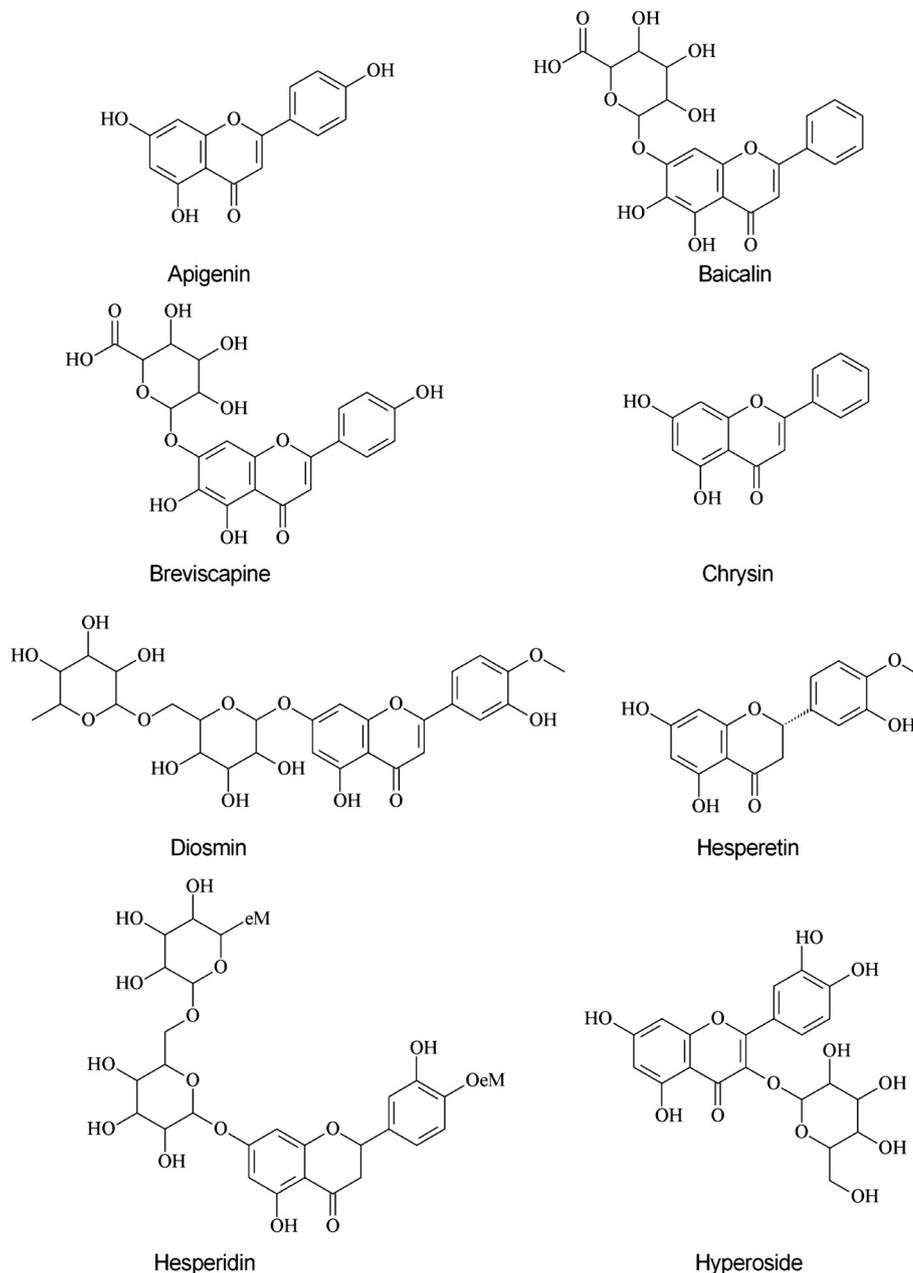
Fig. 2. Structural formula of flavonoids with anti-hepatic fibrosis effects from natural products.

degradation by down-regulating expression of related genes. Li et al. [82] found that tea polyphenols show an anti-fibrosis effect in rats with alcoholic liver disease, and the mechanism may be related to the clearance of overall oxidants and by decreasing endotoxin levels.

3.2. Inhibition of the synthesis of ECM

3.2.1. Inhibition of the activation and proliferation of HSCs

HSCs are the main cells that produce the ECM in hepatic fibrosis [11,14]. A large number of studies have shown that the activation/ proliferation of HSCs and mass generation of the ECM are key links of hepatic fibrosis pathological mechanisms [16,20,24]. Therefore, effective drugs to inhibit the activation and proliferation of HSCs may treat or prevent hepatic fibrosis [39,40]. Wang et al. [24] validated the hypothesis that caffeine inhibits activation of HSCs, which were isolated from a rat ALF model. In this study, this result could be due to caffeine inhibiting the cAMP/PKA/CREB signaling pathway via adenosine A2A

receptors in HSCs (Fig. 1). Jiang et al. [35] demonstrated that *mistletoe* alkaloid fractions decrease ECM accumulation by inhibiting HSC activation. Mechanistically, this may occur via inhibition of TGF-β1/Smad2 and Smad7 signal transduction, thereby blocking the synthesis of procollagen I and TIMP-1, suggesting that *mistletoe* alkaloid fractions may be a potential therapeutic agent for the treatment of hepatic fibrosis. Fucoidan from *F. vesiculosus* inhibits the activation of HSCs and the formation of ECM and autophagosomes, and its effect may be associated with the downregulation of TGF-β1/Smads pathways. Li et al. [40] found that fucoidan, as an autophagy inhibitor and TGF-β1 inhibitor, could be a promising potential therapeutic agent for liver fibrosis. Hesperidin (HDN) is a naturally occurring flavanone glycoside, which is extracted from fruit peels of the *genus citrus*. Lin et al. [51] found that HDND-7, a derivative of HDN, could inhibit the proliferation and activation of PDGF-BB-treated HSC-T6 cells in a time- and dose-dependent manner (Fig. 2). Wang et al. [76] evaluated the cell-killing effect of ursolic acid (UA), a pentacyclic triterpenoid, in activated HSCs
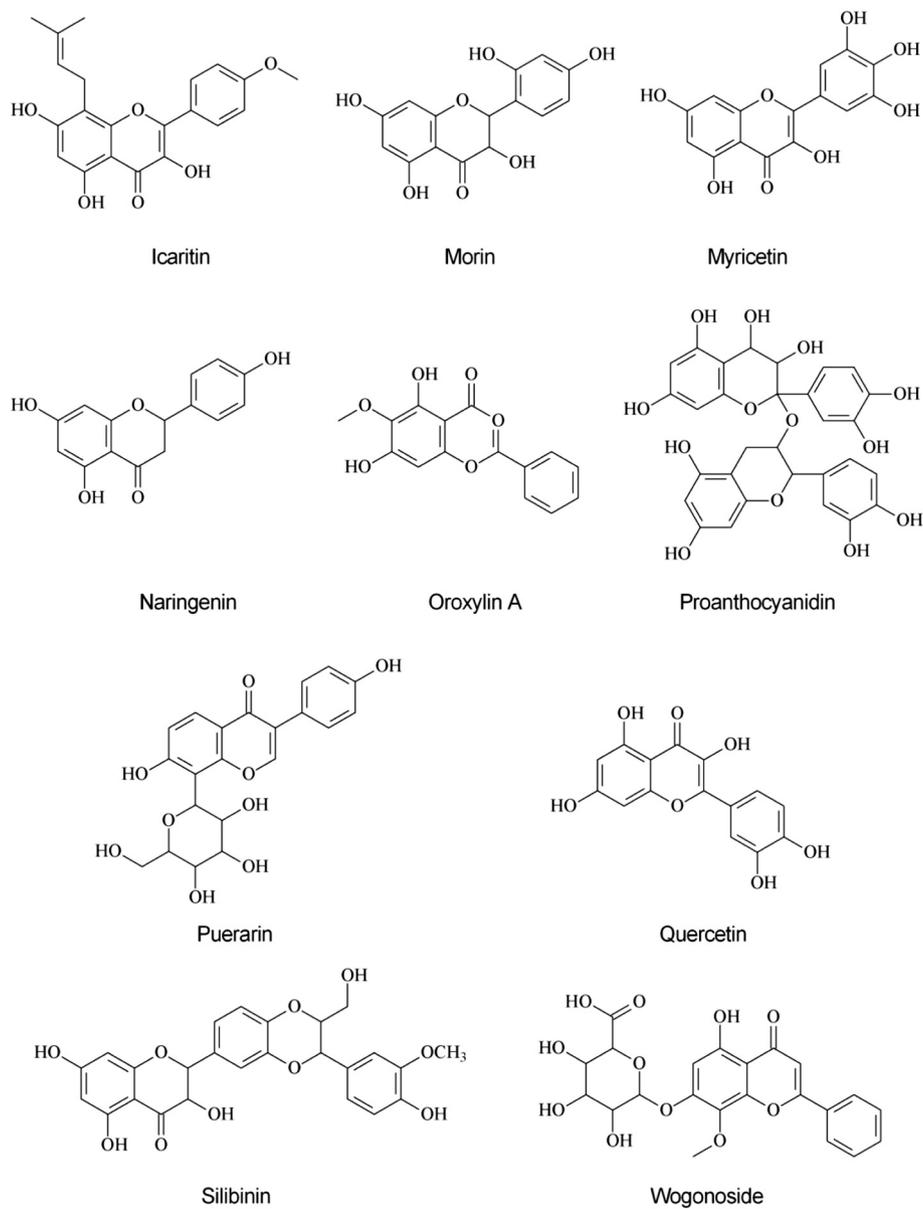
Fig. 3. Structural formula of flavonoids with anti-hepatic fibrosis effects from natural products.

Table 4
Terpenes with anti-hepatic fibrosis function.

Category/active ingredients	Source	Model	Mechanism	References
Monoterpene				
Artesunate	*Artemisia*	A	Inhibition of LPS/TLR4/NF-κB signaling pathway	[71]
Betulinic acid	*Betula platyphylla*	B	Modulating the TLR4/MyD88/NF-κB signaling pathway	[72]
Paeoniflorin	*Paeonia lactiflora*	C	Regulating TGF-β1/Smads signaling pathway	[73]
Total terpenes				
Cucurbitacin-B	*Luffa cylindrica*	A	Inhibition of oxidative stress, inflammation and STAT3 signaling	[74]
Panax notoginseng saponins	*Panax notoginseng*	A	Immunoregulating the imbalance between pro-fibrotic and anti-fibrotic cytokines	[75]
Ursolic acid	*Eriobotrya japonica*	B/D	Specific induction of apoptosis in activated HSCs	[76]

A. CCl$_4$-induced hepatic fibrosis.
B. TAA-induced hepatic fibrosis.
C. radiation-induced hepatic fibrosis.
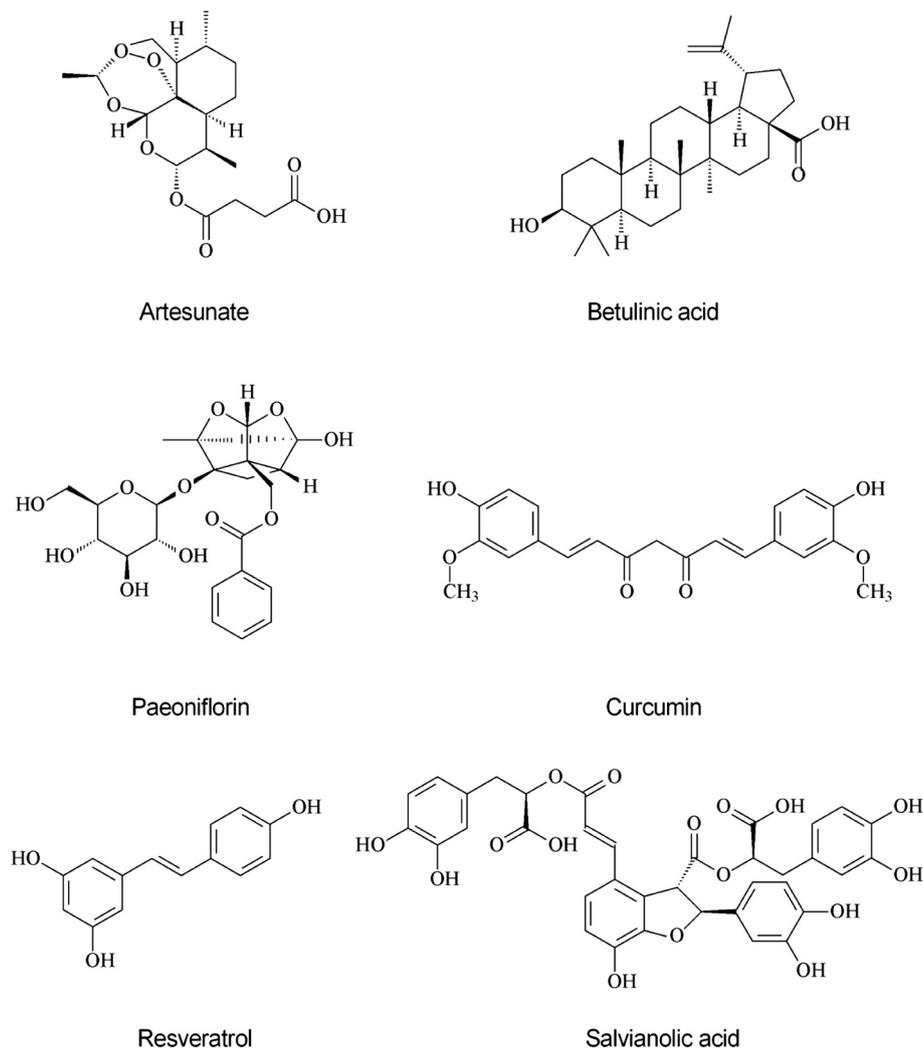D. BDL-induced liver fibrosis.

Fig. 4. Structural formula of terpenes and phenols with anti-hepatic fibrosis effects from natural products.

Table 5
Phenols with anti-hepatic fibrosis function.

Category/active ingredients	Source	Model	Mechanism	References
Single phenol				
Curcumin	*Curcuma longa*	A	Inhibition of the activation of HSCs and induction of their apoptosis	[77]
Resveratrol	*Veratrum nigrum*	A	Reduced collagen-1, TGF-β, NF-κB mRNA expression and desmin and α-SMA protein expression	[78]
Salvianolic acid	*Salvia miltiorrhiza*	A	Suppressed the activation and proliferation of HSCs, inhibition type I collagen and α-SMA	[79]
Total phenols				
Chlorogenic acid	*Lonicera japonica*	A	Through the miR-21-regulated TGFb1/Smad7 signaling pathway	[80]
Ocimum gratissimum polyphenol	*Ocimum gratissimum*	A	Prevents free radical damage and protects liver from oxidative stress	[81]
Tea polyphenols	*Camellia sinensis*	B	The clearance of overall oxidant and decrease of the endotoxin level	[82]

A. CCl_4-induced hepatic fibrosis.
B. alcohol-induced liver fibrosis.

both in vitro and in vivo. UA ameliorated experimental hepatic fibrosis most likely through specific induction of apoptosis in activated HSCs. It is therefore postulated that UA is a potential therapeutic reagent for the resolution of hepatic fibrosis [76]. Shu et al. [77] found that curcumin prevents CCl_4-induced liver fibrosis in rats. The prevention of liver fibrosis may be due to the inhibition of the activation of HSCs and the induction of their apoptosis (Fig. 4).

3.2.2. Modulation of the synthesis and secretion of profibrogenic cytokines

Profibrogenic cytokines play an important role in the occurrence and development of hepatic fibrosis through their signal transduction mechanisms [29,75]. Profibrogenic cytokines secrete a large number of ECM components, leading to fibrosis [31,63]. Yu et al. [29] observed a preventive and modulatory effect of matrine on TGF-β1 and hepatocyte growth factor (HGF) of liver fibrosis tissue in rats and found that matrine reduced TGF-β1 expression and enhanced the activity of HGF, corroborating an inhibitory effect on liver fibrosis in rats (Fig. 1). Chen et al. [31] evaluated the effects of neferine on mice with hepatic fibrosis. The data showed that neferine had an antifibrosis effect on CCl_4-induced hepatic fibrosis in mice, possibly due in part to the decreased expression of TGF-β1 in the liver (Fig. 1). Lin et al. [63] evaluated the therapeutic effects of flavanones from *Sedum sarmentosum Bunge* (FSSB)
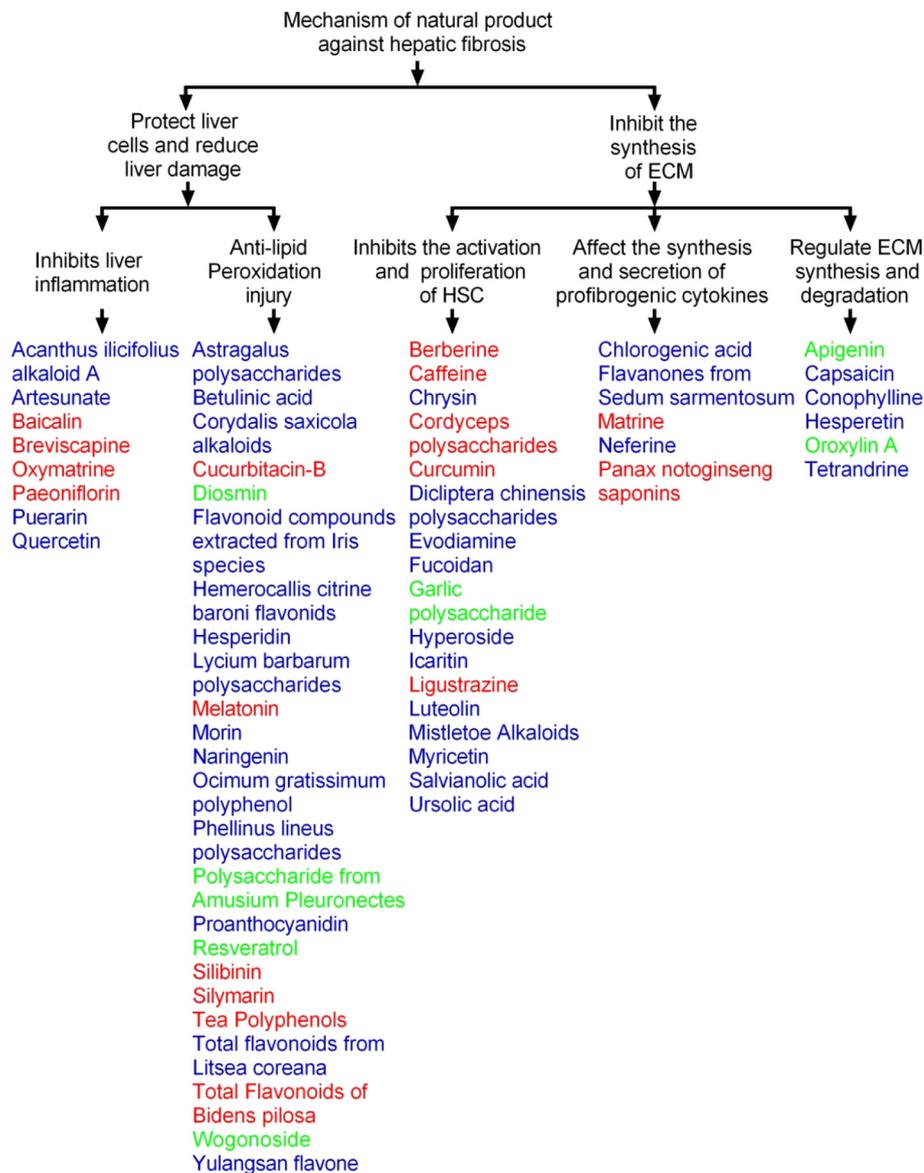
Fig. 5. Anti-hepatic fibrosis mechanisms of 60 natural products. Effects of different natural products are marked in red, blue and green. The natural products of red words have obvious anti-hepatic fibrosis effect and clinical trial results, some of these natural products have preparations marketed at home and abroad. The natural products of blue words have anti-fibrotic effect and preclinical study results, and may be developed as anti-fibrotic drugs. The natural products of green words have anti-fibrotic effect, only part of the experimental results can be found, with bleak prospects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on rats with liver fibrosis. The results suggested that FSSB alleviated CCl₄-induced liver fibrosis through inhibition of the TGF-β/TβR/Smad pathway, which inhibited the epithelial mesenchymal transition [63]. Peng et al. [75] investigated the relationship between the anti-fibrotic effect of *Panax notoginseng* saponins (PNS) and serum cytokines in rat hepatic fibrosis. The experimental results demonstrated that PNS has certain therapeutic effects on hepatic fibrosis, probably by immunoregulating the imbalance between pro-fibrotic and anti-fibrotic cytokines [75]. Chlorogenic acid (CGA) is a phenolic acid that has a wide range of pharmacological effects. Yang et al. [80] explored the effects of CGA in the hepatic stellate LX2 cell line and in CCl₄-induced liver fibrosis in Sprague-Dawley rats. CGA might relieve liver fibrosis through the miR-21-regulated TGF-β1/Smad7 signaling pathway, which suggests that CGA might be a new anti-fibrosis agent that improves liver fibrosis [80] (Fig. 4).

3.2.3. Regulation of ECM synthesis and degradation

Hepatic fibrosis is the undesirable result of excessive deposition of the ECM, and collagen is the main component of the ECM [25,33]. Choi et al. [25] evaluated the inhibitory effects of capsaicin (CPS) on DMN-induced and TGF-β1-induced liver fibrosis in rats and HSCs and found that CPS inhibited DMN-induced hepatotoxicity, NF-κB activation, and

collagen accumulation. The experiment results indicated that CPS ameliorates hepatic fibrosis by inhibiting the TGF-β1/Smad pathway via PPAR-γ activation [25] (Fig. 1). Tetrandrine is an alkaloid isolated from the Chinese medicinal herb, *Stephania tetrandra*. Hsu et al. [33] investigated the in vitro and in vivo effects of tetrandrine on hepatic fibrosis and found that hepatic collagen content of DMN rats was significantly reduced by either tetrandrine or silymarin treatment. In addition, tetrandrine also inhibited TGF-β1-induced α-SMA secretion and collagen deposition in HSC-T6 cells [33] (Fig. 1). Hesperetin, a natural component of *citrus* fruits, is indicated to have beneficial anti-inflammatory effects on injury and various cancers as a TGF-β inhibitor. Kong et al. [50] verified that the favorable role of hesperetin extracted from *citrus* peels could prevent the progression of BDL-induced liver fibrosis via inhibiting TGF-β1/Smad pathway-mediated ECM progression and apoptosis (Fig. 2).

4. Discussion

In recent years, the treatment of hepatic fibrosis has developed from anti-inflammatory treatment to multi-modality treatment targeting HSCs to inhibit the formation of collagen fibers and promote the degradation of collagen [83,84]. At present, most of these drugs are still at
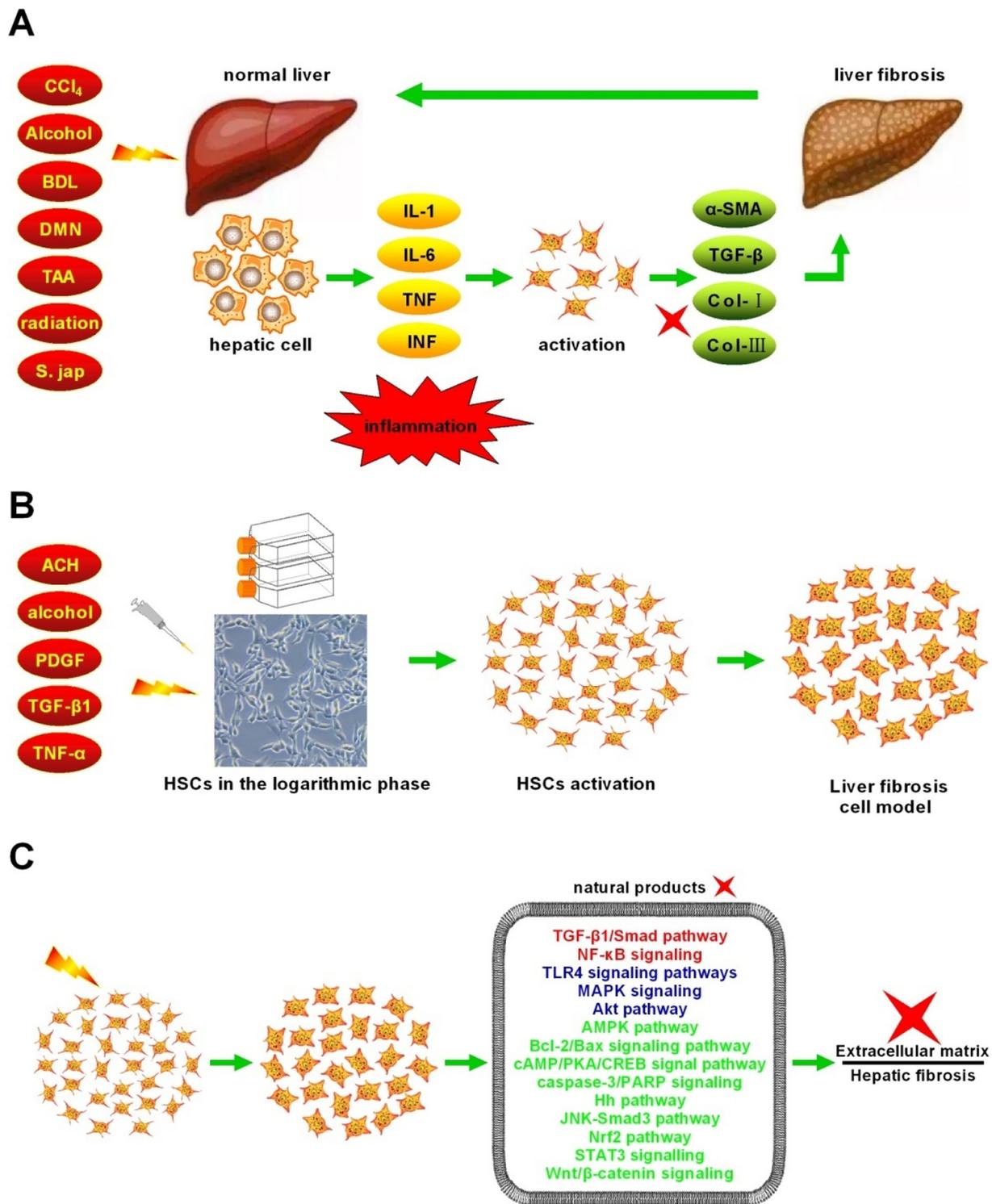
Fig. 6. Animal models, cell models and signaling pathways involved in the study of natural products with anti-hepatic fibrosis effect. (A). Animal models used in the study of hepatic fibrosis. (B). Cell models used in the study of hepatic fibrosis. (C). Signaling pathways involved in the study of the mechanisms of natural products with anti-hepatic fibrosis. The anti-hepatic fibrosis mechanism of most natural products are related to the 2 signaling pathways marked red words. Some are related to the 3 signaling pathways marked blue words. A few are related to the 9 signaling pathways marked green words. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the stage of preclinical experimental research, few have been clinically verified, and even fewer have been clinically proven to be effective [85,86]. Preventing the formation and progression of hepatic fibrosis is of great significance in preventing and treating hepatic cirrhosis [87,88]. Professor Popper, a famous scholar, once stressed that preventing or delaying the occurrence of hepatic fibrosis will likely cure

most chronic hepatic diseases. However, there is still a lack of ideal drugs for the treatment of chronic liver fibrosis [89–91]. Optimal anti-hepatic fibrosis drugs should satisfy the following conditions: (1) drug activity should be limited only to the liver, (2) its effects must be directed against collagen or other key components of the ECM, and (3) drugs should be non-toxic [92,93]. Therefore, efforts should be made to

develop new drugs targeting hepatic fibrosis in these directions [94,95].

At present, there are many reports on anti-hepatic fibrosis drugs, but few have been converted into novel clinical drugs [96,97]. One of the major reasons for this is that there is a substantial difference between animal models and human hepatic fibrosis disease pathogenesis, resulting in a gap between animal experiments and clinical efficacies [98,99]. Additionally, hepatic fibrosis is a complex pathological process with dynamic changes that involve multiple links and factors [100,101]. It is difficult to solve complicated hepatic fibrosis by only a single natural compound [102,103]. Excitingly, the achievements of TCM in the fight against hepatic fibrosis have attracted the interest of American medical institutions and scholars [104,105]. An FDA-approved TCM Fuzhenghuayu formula has entered the West from the East, and phase II clinical trials have been completed with promising results [106].

In recent years, active ingredients from natural products with anti-hepatic fibrosis properties have shown relatively broad prospects. Some progress has been made in research on anti-hepatic fibrosis effects and mechanisms. However, much work remains, such as identifying the active ingredients of natural products, the mutual compatibility relations between active ingredients, the active ingredients of targets and molecular mechanisms through large-scale, multi-center, randomized, double-blind studies [107,108]. In summary, addressing liver fibrosis disease is a much needed task, and it clearly requires considerable effort in basic and clinical research to identify and verify new drug targets and initiate novel drug developments [109,110].

In this study, we analyze and summarize 60 natural products with anti-hepatic fibrosis effect over the past decade. The pharmacological functions of natural products include multiple-treatment effects against various systematic diseases, including cardiovascular, neurological, immunological, endocrinology, and respiratory symptoms [64]. Chen et al. had reviewed the natural products against liver fibrosis in 2015, but the main content was to summarize the research results before 2015 [10]. We summarize the research progress of natural products with anti-fibrotic effect in recent 10 years, including 26 kinds of flavonoids, 14 kinds of alkaloids, 8 kinds of polysaccharides, 6 kinds of terpenes and 6 kinds of phenols. We find that some natural products have better anti-liver fibrosis effect, and there are many studies on them, such as Matrine, Oxymatrine, Silymarin, Silibinin, Melatonin, Paeoniflorin, Caffeine, Cordyceps polysaccharides, Breviscapine, etc. (see the red part of Fig. 5, a total of 17). And some preparations of these natural products have been used in clinical practice at home and abroad [29,61,67]. Blue part of Fig. 5 has 36 natural products, which are found to have anti-liver fibrosis effect at present, and some of them have clinical research results, which may be developed into anti-liver fibrosis drugs [38,51,68]. Among these natural products, *Dicliptera chinensis* polysaccharides, Puerarin, Proanthocyanidin, Hesperidin and its derivatives, Total Flavonoids of *Bidens bipinnata*, Yulangsan flavones, Total flavonoids from *Litsea coreana*, etc. have been extensively studied. Green part of Fig. 5 has 7 natural products, currently, there are only few research data about these natural products, with only few research results and unclear prospects [41,44,78].

The present results indicate that the anti-hepatic fibrosis mechanisms of natural products mainly include anti-lipid peroxidation injury (24 kinds) and inhibition of activation and proliferation of HSCs (17 kinds) (Fig. 5). Some natural products resist liver fibrosis by inhibition liver inflammation (8 kinds), modulation of the synthesis and secretion of profibrogenic cytokines (5 kinds) and regulation of ECM synthesis and degradation (6 kinds) (Fig. 5). We find that the anti-liver fibrosis effect of most natural products are related to anti-lipid peroxidation injury, which are consistent with the findings of Lin et al. [111]. Animal and cell models of liver fibrosis are shown in Fig. 6A and B. On the other hand, we summarize all 60 natural products with anti-hepatic fibrosis effect in 61 references, and find that 14 signaling pathways are involved in the anti-hepatic fibrosis process of natural products (Fig. 6C), most of which are associated with TGF-β1/Smad pathway and

NF-κB signaling pathway [25,50,69]. Of the 60 natural products listed from reference 22 to reference 82 in this paper, 19 are related to TGF-β1/Smad pathway, and 9 are related to NF-κB signaling pathway [27,52,71]. Chen et al.'s review has a detailed description of TGF-β1/Smad pathway and NF-κB signaling pathway, including diagram [10]. In addition, some literatures involve the 3 pathways of the blue part [32,60,62]. Finally, the 9 pathways of the green part are less involved in the current research [23,28,74] (Fig. 6C). In a word, the mechanisms of natural products on anti-liver fibrosis are complex, and the mechanisms of some natural products with anti-liver fibrosis effect involve multiple aspects and multiple pathways, which are the results of comprehensive effects and still need to be further studied.

At present, the research on natural products with anti-hepatic fibrosis effect needs to be improved. Firstly, there are few studies on the structure-activity relationship of natural products with anti-liver fibrosis effect, and the results are not clear. In addition, epigenetics has developed rapidly in recent years, and there are few epigenetics studies on natural products with anti-liver fibrosis effect [79]. Moreover, there are few potential targets for anti-hepatic fibrosis. So far, only three new potential targets have been identified, namely PPAR pathway, Hedgehog (Hh) pathway and telomerase [49,79,112]. Finally, most of the current studies on the mechanism are focused on one signal pathway, and there are few literatures involving multiple pathways, and there is no figure reflecting the common signal pathway of liver fibrosis. In summary, the study of natural products with anti-hepatic fibrosis effect is getting more and more in-depth.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

Funding

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