PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2020,47(8):790~808
www.pibb.ac.cn

Treatment of Liver Fibrosis Using Traditional Chinese Medicine Through Anti-inflammatory Mechanism*

LI Bo[1,2)**], FENG Wen-Tao[1)], LI Jing-Yi[1)], LI Tian-Mei[1)], CAO Yan-Lu[1)], LÜ Fang[1)], DAI Rong-Ji[1)**], DENG Yu-Lin[1)**]

([1)]*Beijing Key Laboratory for Separation and Analysis in Biomedicine and Pharmaceuticals, School of Life Science, Beijing Institute of Technology, Beijing* 100081, China;
[2)]*Advanced Research Institute of Multidisciplinary Science, Beijing Institute of Technology, Beijing* 100081, China)

Abstract Liver is the largest substantial organ in the abdominal cavity and it provides an essential role in maintaining the basic physiological functions. Liver diseases have become one of the common and frequently-occurring diseases that affect 10% of the population worldwide, usually with liver fibrosis as the late stage pathological characteristic. Due to the complexity of pathogenesis, there is no effective synthetic drug to treat liver fibrosis up to date. Traditional Chinese medicine (TCM) has the advantages of multiple targets and small side effects in the treatment of liver fibrosis. This article reviews the pathological mechanisms of liver fibrosis and its relationship with inflammation. The application of the active herbal ingredients in TCM, medicinal plants and traditional Chinese formulae to treat liver fibrosis, and their mechanisms of action to inhibit inflammation associated with liver fibrosis are also discussed.

Key words liver fibrosis, traditional Chinese medicine, anti-inflammation treatment, mechanism of action
DOI: 10.16476/j.pibb.2020.0183

1 Pathogenesis of liver fibrosis

Liver is the largest substantial organ in the abdominal cavity. It carries out about 500 distinct roles with its main job to filter the blood coming from the digestive tract before passing it to the rest of the body. Liver also synthesizes functional proteins, detoxifies chemicals, produces chemicals that digest food and metabolize drugs. Liver damages usually include fatty liver with increased triglyceride[1], chemical liver injury[2], immune liver injury[3], drug induced and alcohol induced liver injury[4], *etc*. Liver diseases have become one of the major diseases threatening the human health. The number of patients suffered from liver diseases is as high as 1.3 billion worldwide, among which about one third of the population are Chinese.

Liver fibrosis is a dynamic, highly integrated process involving mechanisms on molecular, cellular and tissue levels[5]. The external causes of liver fibrosis include hepatitis C virus (HCV) infection, Hepatitis B Virus (HBV), addiction to alcohol, nonalcoholic steatohepatitis (NASH) and drug-induced liver injury, *etc*. Among them, HBV infection remains a major health problem worldwide despite the availability of a highly effective preventive vaccine. HBV, HCV, and drug-induced liver damage can cause liver inflammation, which leads to repeated healing damage and finally liver fibrosis[6]. The internal causes of liver fibrosis are mainly chronic damage of liver and the accumulation of extracellular matrix proteins (ECMs). The late stage of liver fibrosis may

* This work was supported by a grant from the Beijing Institute of Technology Research Fund Program for Young Scholars.
** Corresponding author.
LI Bo. Tel: 86-10-68913188, E-mail: boli@bit.edu.cn
DAI Rong-Ji. Tel: 86-10-68913310, E-mail: dairongji@bit.edu.cn
DENG Yu-Lin. Tel: 86-10-68914907, E-mail: deng@bit.edu.cn
Received: June 1, 2020 Accepted: June 9, 2020

develop into liver cirrhosis, liver failure, and liver cancer. Liver fibrosis is reversible in the pathological process, therefore, how to effectively slow down or inhibit the progression of liver fibrosis and reverse its symptom has become a major concern to treat liver diseases.

Traditional Chinese medicine (TCM) is a great treasure in the history of pharmacology with its history of more than 3 000 years. From the earliest "The Inner Canon of Yellow Emperor", "The Holy Husbandman's Classic on Roots and Herbs" to the "Compendium of Materia Medica", TCM has drawn great attention all over the world. In the past few decades, the effect of TCM is widely well recognized for the treatment of a wide range of diseases[7]. In Western countries, it is also common to add natural herbs to drugs and dietary supplements. Due to the complexity of pathogenesis, there is no effective synthetic drug to treat liver fibrosis up to date. On the other hand, TCM has been used to treat liver disease for a long time because of its advantages of multiple targets and small side effects.

From the perspective of TCM, the pathology of liver fibrosis is mainly due to dampness, heat, and stasis. Poison and deficiency of righteousness are intricately compounded and combined in the liver, which will eventually form liver fibrosis. The main pathogenic factor of liver fibrosis is dampness and heat, with blood stasis as an important pathological result and the key link of the pathogenesis[8]. Therefore, the single and compound prescriptions of Chinese medicine formula to treat liver fibrosis are focused on blood-activating, heat-clearing and deficiency-supplementing.

From the perspective of Western medicine, liver fibrosis is the result of healing from repeated liver injury in a long term. As shown in Figure 1, upon external factors such as viral infection, excessive alcohol consumption or chemicals attack, liver cells are damaged or even undergo apoptosis and necrosis. Compared to normal liver, there is a large amount of fibrous tissue proliferation and deposition in the fibrotic liver. Kuffer cells are regenerated to replace the necrotic and apoptotic liver cells. This process is accompanied by the inflammatory response and limited ECM deposition. If the hepatic cells are continued to be damaged, the regeneration will eventually fail. Liver cells are replaced by the abundant ECMs including fibrillar collagen[9]. With the continuous damage of liver cells, apoptosis and two hits, liver fibrosis is gradually formed. The deterioration of liver fibrosis will eventually lead to irreversible liver cirrhosis and liver cancer.

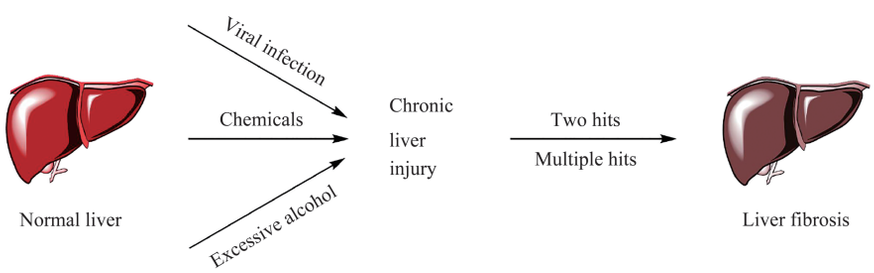

Fig. 1 The progress of liver fibrosis

Hepatic stellate cells (HSCs) play a crucial role in the progress of chronic liver fibrosis. Bone marrow-derived fibrocytes, epithelial-to-mesenchymal transformation, and portal fibroblasts (Pfb) also promote liver fibrosis, but relatively smaller compared to the effect of HSCs. In the damaged liver, HSCs are the major cells producing ECM cells[10]. In normal liver cells, HSCs are present in Disse, and are mainly used to store vitamin A. As shown in Figure 2, upon the stimulation of external factors, kupffer cells release transforming growth factor beta 1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), reactive oxygen species (ROS) and other cytokines through stimulation of the TLR4-CD14 pathway. Damaged hepatocytes release insulin-like growth factor 1 (IGF1), TGF- β, TNF- α, ROS and other cytokines. Biliary epithelial cells release platelet-derived growth factor (PDGF), IL-6, TGF-β and other cytokines. T cells release cluster of differentiation 40 protein (CD40), IL-6, interferon gamma (IFN-γ) and

chemokine (C-C motif) ligand 21 (CCL21). The quiescent HSCs are activated by a variety of cytokines upon external stimulation[11]. A large number of activated HSCs differentiate into myofibroblasts, and activation of myofibroblasts is an important hallmark of liver fibrosis[12]. Myofibroblasts release TGF-β, alpha-smooth muscle actin (α-SMA) and fibronectin. In addition, the decreased secretion of matrix metalloproteinases (MMP)-1/3/9/13 and the increased secretion of tissue inhibitor of metalloproteinases (TIMPs)-1/2/3 result in large accumulation of ECM leading to hepatocyte necrosis or apoptosis[13]. Another part of HSC cells release TGF-β, α-SMA, IL-6, interleukin 8 (IL-8) and other cytokines to induce hepatocyte apoptosis. With the continuous accumulation of ECM and the gradual apoptosis of hepatocytes, liver fibers are transformed into irreversible cirrhosis and even liver cancer.

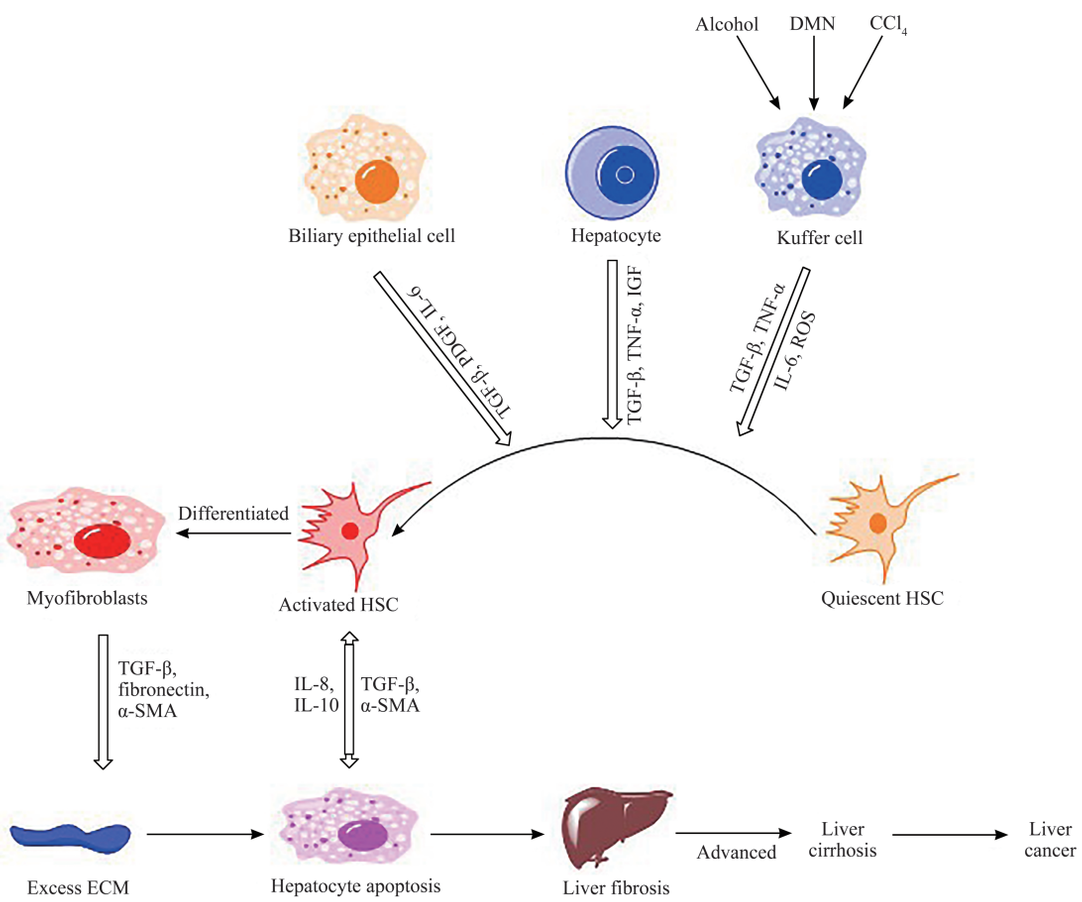

Fig. 2 The mechanism pathways involved in the liver fibrosis formation

2 Inflammatory pathways and factors associated with liver fibrosis

From the perspective of Western medicine, inflammation is a basic pathological process in which biological tissues are stimulated by various external or internal stimuli such as trauma, infection and other damage factors. Local manifestations of inflammation include redness, swelling, heat, pain, dysfunction, as well as systemic reactions such as fever and changes in peripheral white blood cell counts. The main causes of inflammation include biological factors (such as bacteria, viruses, rickettsia, mycoplasma, fungi), physical factors (such as high temperature, low temperature, radioactive materials, mechanical damage), chemical factors (such as strong acid, strong alkali, decomposition products of necrotic tissue), foreign bodies (such as surgical sutures, foreign bodies entering the human body through various means), necrotic tissue and allergic reactions. Often, inflammation is the body's automatic defense response

although the patients may feel pain or other discomfort symptoms, but it is beneficial for health. However, sometimes inflammation is harmful, such as attacking on the body's own tissues, inflammation occurred in transparent tissues, and inflammatory reactions associated with liver fibrosis.

Inflammation can be divided into two major categories—acute and chronic inflammation—based on timing and pathological features. Acute inflammation is typically of relatively short duration (hours to days) and is characterized by vasodilatation, the exudation of protein-rich fluid (plasma), a migration of cells (primarily neutrophils) into the site of injury and, in some cases, activation of the coagulation cascade[14]. Atherosclerosis, inflammatory bowel disease and liver fibrosis are involved with typical histological features of chronic inflammation. These disorders are characterized by a prolonged duration (weeks to months to years) in which active inflammation, tissue destruction and attempts at tissue repair are occurring simultaneously[15].

In general, inflammation is a special, self-controlled, self-defense response to the infection or tissue repair. However, inflammation can produce an unbalanced response that is associated with steady-state destruction of physiological processes and is not directly related to classical inflammation triggers[16]. When the triggering factor is not contained, it triggers a dysfunctional inflammatory response and causes chronic damage to the tissue, leading to inflammatory diseases such as chronic liver disease including liver fibrosis[17].

Inflammatory cytokine signalings involved in liver fibrosis include transduction of cytoplasmic and nuclear signaling mechanisms leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the c-Jun N-terminal kinase (JNK), P38 mitogen-activated protein kinases (p38 MAPK), signal transducer and activator of transcription 3 (STAT3), and the phosphoinositide 3-kinases (PI3K) pathways[18].

NF-κB plays an important role in the activation of inflammasomes by stimulating the expression of pro-inflammatory genes. NF-κB is also a central inflammatory mediator in response to a variety of immune receptors that promote the initiation and development of various inflammatory diseases including liver fibrosis[19]. JNKs and p38 MAPK are a subgroup of the mitogen-activated protein kinase (MAPKs) family. The main targets of JNKs are transcription factor AP-1 (mainly c-Jun), c-Myc, p53, and non-transcription factor Bcl-2. JNKs are essentially involved in the process of apoptosis and cell death triggered by a variety of stimuli including UV radiation, cytokines and cancer[20]. STAT3 is a pleiotropic transcription factor that regulates signal transduction of cytokines, growth factors and oncogenes. It functions both as a typical transcriptional activator, atypical energy metabolism and mitochondrial function regulators[21]. PI3K signaling pathway regulates cell proliferation, survival and metabolism. Akt (also known as protein kinase B) is a key downstream in PI3K signaling pathway and plays an important role in cell survival and apoptosis.

The inflammatory response plays a crucial role in the progression of liver fibrosis. As shown in Figure 3, under the induction of external factors such as HCV, hepatitis B virus (HBV) and lipopolysaccharides (LPS), kuffer cells (KC) secrete TNF-α and interleukin 1 (IL-1) which activate the IκB kinase (IKK) complex. The complex phosphorylates IκB, which leads to the degradation of IκB's proteasomal, allows NF-κB to enter the nucleus to initiate transcription of the target gene[22]. Through this pathway, TNF-α, IL-1β, IL-6 are secreted to activate HSC. In addition, the activated NF-κB pathway activates high mobility groupbox 1 (HMGB1), increases secretion of toll-like receptors (TLRs), activates macrophages therefore triggers inflammation[23]. Addition to the major NF-κB pathway, KCs secrete TNF-α and TGF-β, which interact with JNK and p38 MAPK signaling pathways, respectively, causing ROS accumulation and the secretion of collagen I[18]. Activated macrophages and HSCs secrete IL-6 and interleukin 17 (IL-17), respectively, activating the STAT3 signaling pathway to further promote inflammatory responses.

The process of liver fibrosis is the result of a variety of cellular crosstalks. Different cells release different inflammatory factors, activate related pathways, promote inflammatory reactions, and ultimately lead to liver fibrosis. As shown in Figure 4, the most important process of liver fibrosis is the activation of HSCs. Accompanying the progress of liver fibrosis, multiple cells release various factors to promote HSC activation and proliferation. The progenitor cells activate KCs under the control of

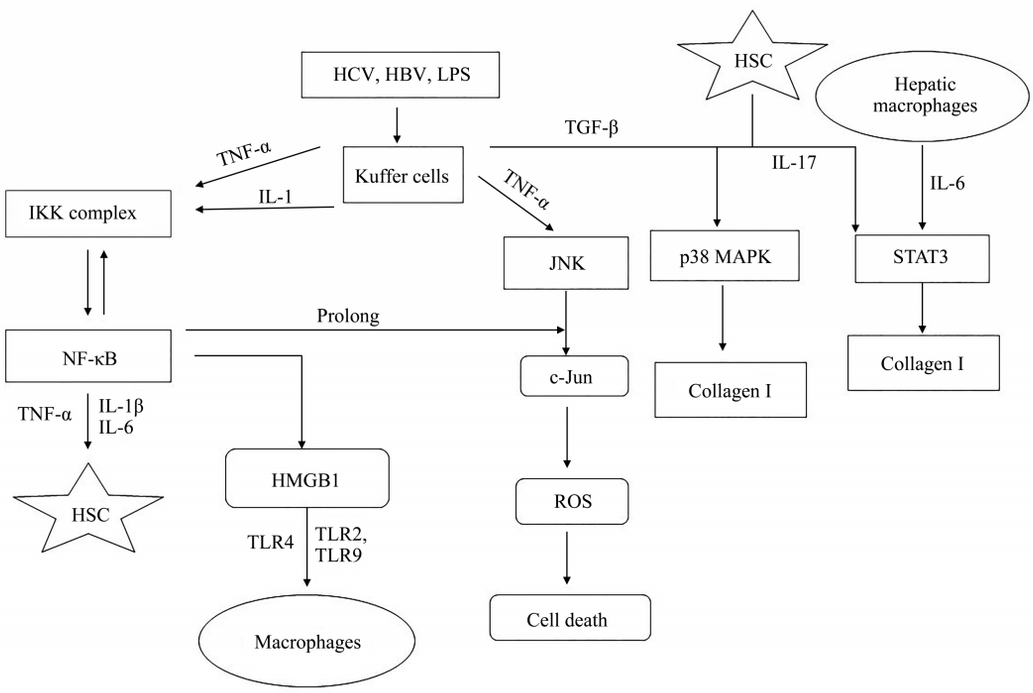

Fig. 3　The inflammatory pathways associated with liver fibrosis

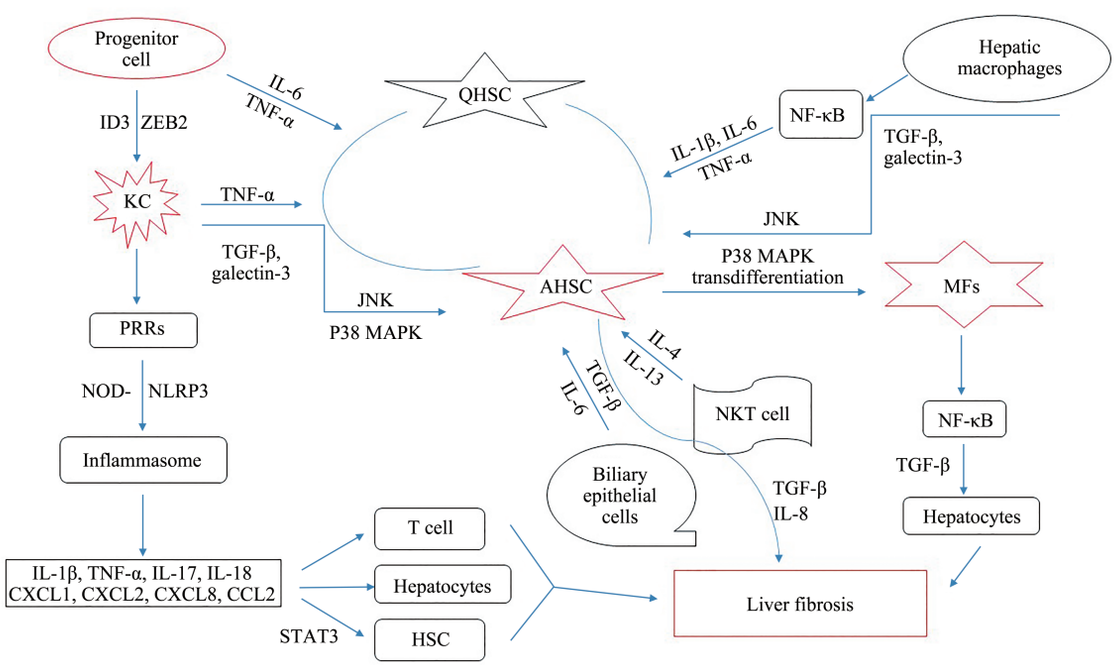

Fig. 4　Crosstalk associated with liver fibrosis

transcription factors ID3 and ZEB2. Particle progenitor cells directly secrete cytokines IL-6 and TNF-α, which activate HSCs. After activation, KC cells activate pattern recognition receptors (PRRs) through various protein complexes such as nucleotide oligomerization domain (NOD-), leucine-rich repeat (LRR-), nod-like receptors pyrin domain containing 3 (NLRP3) under the NF-κB pathway, resulting in the

formation of inflammasomes[24]. Inflammasomes release IL series, TNF-α, C-X-C motif chemokine ligand (CXCL) series, C-C motif chemokine ligand 2 (CCL2) and other cytokines to activate T cells, HSCs, and damage liver cells. KC cells secrete TGF-β and galectin-3 activating HSCs (AHSCs) through JNK and p38 MAPK pathway to promote its proliferation and differentiation into myofibroblasts (MFs). In addition, hepatic macrophages secrete IL-1β, IL-6 and TNF-α to activate HSCs through NF-κB pathway. Hepatic macrophages also secrete TGF-β and alectin-3 to promote proliferation and differentiation of HSCs. Other cells, such as biliary epithelial cells, secrete IL-6, TGF-β to activate HSCs. Natural killer T (NKT) cells secrete IL-4 and IL-13 to activate HSCs[25]. After activation, HSCs secrete IL-8 and α-SMA causing damage to hepatocytes, gradually leading to liver fibrosis. All of the above mentioned signaling pathways and cytokines interact with each other influencing the progression of liver fibrosis.

3 Traditional Chinese medicine to treat liver fibrosis through anti−inflammatory mechanism

In recent years, studies have found that a variety of cytokines, growth factors, chemokines are involved in the formation of liver fibrosis[26-27]. According to their functions, cytokines participate in the formation and development of liver fibrosis can be divided into pro-fibrotic factors and anti-fibrotic factors. The development of effective anti-fibrosis drugs has been focused on the occurrence mechanism of liver fibrosis, including anti-fibrotic factors, blocking the signaling pathway during the formation of liver fibrosis and blocking the deterioration from liver fibrosis to liver cirrhosis and liver cancer. The efficacy of synthetic drugs to treat liver fibrosis is not outstanding, and the price of drugs is relatively high. In addition, side effects are usually a big problem of synthetic drugs. Therefore, it has been focused on TCM to treat liver fibrosis due to their multi-active ingredients and multi-targeting functions.

Inflammation plays a very important role in the pathological process of liver fibrosis. Under external stimulation or internal bacterial infection, KC cells alternate and this process releases IL-1α, a marker of acute inflammation[28], causing acute inflammation in the liver. This process results in increased vascular permeability of the liver and infiltration of neutrophils as well as phagocytes, corresponding to the exudation stage. Exudation leads to the activation of HSCs and further release of inflammatory factors IL-1β, TNF-α, *etc*., leading to the apoptosis of hepatocytes and more inflammatory response. In this process, proliferation of inflammatory cells occurs and acute inflammation gradually transits to chronic inflammation, corresponding to the proliferation stage. Within this stage, accumulation of extracellular matrix proteins, repeated hepatocyte damage and repair influence each other leading to the gradual formation of liver fibrosis[29]. The specific signals induced by specific inflammatory factors lead to the proliferation and aggregation of the phagocytic immune cells. These immune cells secrete and produce pro-inflammatory factors and chemokines which induce lymphocytes to produce adaptive immune response. During the inflammatory immune response, ROS, reactive nitrogen species (RNS) and different proteases can cause tissue damage, fibrosis, and cell proliferation, which lead to the long-term inflammation. This process will render the liver fibrosis worse and develop into cirrhosis and even liver cancer eventually.

From the perspective of Chinese medicine, inflammation mostly falls under the category of Chinese medicinal "fire" and "heat". The acute inflammation is mostly due to "yang" and "heat", and the treatment is often focused on driving away "heat" and detoxify the body. The slow lingering inflammation is mostly chronic inflammation with hidden, slow and prolonged symptoms. To determine the severity of inflammation, if the disease is less severe in the "Wei-Qi" and the "six viscera", the disease is more severe in the blood and the organs. Acute inflammation is characterized by "Stagnant Qi", which is usually treated by adjusting and de-stressing the "Qi" mechanism, but not by replenishing it (unless the deficiency is more obvious). "Qi stagnation" and blood stasis is one of the basic pathologies of inflammation, and the reasoning of "Qi" revitalization and dispelling of blood stasis is also one of the basic treatment of inflammation. Therefore, it has been focused on blood circulation and expectorant stasis to treat inflammation in Chinese medicine. Chronic inflammatory disease is a long-lasting disease that is repeatedly prolonged, the cause of which is the dampness of the inflammatory disease[30].

It is believed that liver fibrosis treatment through

anti-inflammation should be focused on promoting the blood circulation to remove blood stasis from the perspective of TCM. An important target direction for the treatment of liver fibrosis is searching for appropriate anti-inflammatory agents. Up to date, *Ylangsan*, *Bupleurum*, *Peach Kernel*, *Dendrobium Huoshan*, *Schisandrae*, *Cordyceps Sinensis*, *Safflower*, *Astragalus*, *Atractylodes*, *Matrine* and some other TCMs have been reported to exhibit effective anti-fibrosis activities. Chinese herbal medicine compound such as *GanNingPian*, *FuZhengHuaYuFang*, *BaoGanYiHao*, *XiaYuXueTang* and *FuFangBieJiaRuanGanPian* showed effective anti-liver fibrosis *in vitro*, *in vivo* and in the clinical experiments. Herein, we reviewed the active ingredients in the TCM, the natural herbal plants, and effective Chinese medicine formulae to treat liver fibrosis and their mechanism of action focusing on their anti-inflammation activities and mechanisms.

3.1 Natural ingredients in traditional Chinese medicine to treat liver fibrosis through anti−inflammatory pathways

The early stage of liver fibrosis is reversible involving with initial acute inflammation followed by long term chronic inflammation in the late stage of liver fibrosis. Lots of active ingredients in TCM have been discovered to exhibit anti-inflammatory effects which provide effective treatment for liver fibrosis.

Phenanthrene derivatives are widely distributed in nature, mainly in plants Orchidaceae, Juncaceae and Dioscoreaceae. They provide anti-inflammatory and antioxidative effects, therefore providing potential anti-liver fibrosis effect. Natural 5, 7-dimethoxy-1, 4-phenanthrenequinone (CLLV-1) (compound 1 in Table S1) inhibits neutrophil activation by inhibiting phosphorylation in the PKB/AKT pathway. It also reduces ROS accumulation and inflammatory damage and provides potential anti-fibrosis activity[31]. Dioscoreanone (compound 2 in Table S1) inhibits the activation of NF- κB pathway by inhibiting the degradation of IκBα, reducing the release of inflammatory factors IL-1β and IL-6, providing the potential anti-fibrosis activity[32]. Phenanthrene derivative compound 3 (Table S1) increases the expression of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and the downstream heme oxygenase-1(HO-1) through the NF- κB pathway. It also reduces the expression of iNOS, COX-2 and other inflammatory factors providing potential anti-fibrosis effect[33]. Phenanthrene derivative compound 4 (Table S1) can inhibit the activation of p38/MAPK pathway, reduce the accumulation of ROS, thereby it reduces inflammatory damage providing potential anti-fibrosis effect[34]. Phenanthro[9, 10-b]furan-3-one derivatives (compound 5 and 6 in Table S1) inhibit the activity of COX-2 providing anti-inflammatory effects[35]. The other six phenanthrene derivatives (compounds 7−12 in Table S1) inhibit NO production and reduce inflammation[36]. Ephemeranthol A (compound 13 in Table S1) and dehydroorchinol (compound 14 in Table S1) decrease the secretion of NO, COX-2, IL-6, IL-1β and TNF-α by blocking the NF-κB pathway and phosphorylation of the phagocytic MAPK pathway, therefore decrease the inflammatory response associated with liver fibrosis[37]. Batatasin I (compound 15 in Table S1), a phenanthrene derivative extracted from tuberous Roots of Dioscorea Batatas., reduces COX-2 release and improves inflammatory response[38]. Compound 16 in Table S1 inhibits the LPS-induced, toll receptor-mediated activation of the NF- κB pathway and reduces the release of TNF- α, COX-2, IL-8 and IL-1β, providing potential anti-fibrosis effects[39].

Resveratrol (compound 17 in Table S1) is a natural phenolic flavonoid found in grapes, peanuts, berries, nuts and it provides many biological activities[40]. It is reported that resveratrol can reduce both acute inflammation and chronic inflammation[41-42]. It increases the production of endogenous anti-inflammatory cytokine interleukin 10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF). Resveratrol also promotes the reprogramming of macrophages M to the anti-inflammatory interleukin 4 (IL-4). In addition, it promotes the release of inflammatory cytokines and chemokines including TNF- α, anti-inflammatory cytokine interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP1), one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Therefore, resveratrol accelerates the destruction of pathogens and promotes the recovery of liver.

Cannabidiol (CBD) (compound 18 in Table S1) is an active ingredient in *Cannabis* that has shown protection effect of liver. Cannabidiol can significantly inhibit the translocation of NF-κB p65. It also inhibits the nucleotide binding domain such as

receptor protein 3 (NLRP3) inflammasome, resulting in a decreased expression of inflammation related factors[43].

Gastrodia elata (GE) (compound 19 in Table S1) is a natural compound used to treat and prevent liver fibrosis. In TCM, GE is also used to treat various diseases such as headache, dizziness, cramps and convulsions. The various medicinal effects of GE have been scientifically proved including antioxidant, anti-inflammatory, anti-convulsant and anti-epileptic. It has been found that GE can improve liver function and histopathology, and its mechanism is related to the ability to inhibit inflammation by inhibition of NF-κB signaling pathway[44]. Later research found that GE can activate PI3-K/Akt signaling, decrease the expression of inflammatory cytokines iNOS, COX-2, TNF-α and IL-6 by inhibition of NF-κB and MAPKs signaling pathway[45] providing the anti-inflammatory effects.

Yangonin (compound 20 in Table S1) is a natural product isolated from *Kava*, a perennial tropical shrub that is widely cultivated in the South Pacific island[46]. It has been found that Yangonin inhibits liver fibrosis induced by thioacetamide (TAA) in mice. By measuring the genes associated with inflammation, TAA induces the expression of TNF-α, IL-6 and IL-1 in the liver, while Yangonin treatment significantly reduces the level of these inflammatory genes by regulation of NF-κB[47] pathway.

Uroslic acid (compound 21 in Table S1) is a pentacyclic triterpenoid compound extracted from berries, leaves, flowers and other fruits such as *Rosmarinus Offificinalis*, *Eriobotrya Japonica*, *Crataegus Pinnatififida*, *Ocimum Sanctum*, and *Eugenia Jambolana*. Uroslic acid has been reported to protect against liver damage caused by exogenous organisms and induce apoptosis of activated HSCs both *in vitro* and *in vivo*. Although its molecular mechanism of action requires further investigation, it is speculated that uroslic acid may inhibit NF-κB and Akt-mediated cell survival signals, leading to the activation of mitochondrial permeability transition pores (MPT) and downstream caspases, resulting in the apoptosis of activated HSCs therefore inhibits liver fibrosis[48].

Glycyrrhizin (GL) (compound 22 in Table S1), also named as glycyrrhizic acid, is a major bioactive triterpene glycoside containing an 18-β-H-oleanane-type structure with two glucuronic acids at the C-3 position[49]. GL has a variety of pharmacological activities and is currently used for the treatment of chronic hepatitis C and human virus infections in clinical practice, providing potential anti-liver fibrosis activities. GL significantly inhibits ROS production, reduces mitochondrial damage and inflammatory responses by activating Nrf2 and increasing downstream HO-1 expression[50]. GL can also inhibit HMGB1 and TLR4, block the activation of NF-κB, increase bile secretion, thereby reduce inflammation[51].

Naringin (4′, 5, 7-trihydroxyflavone-7-rhamno-glucoside) (compound 23 in Table S1), a natural product abundant in grapes and related citrus species[52], has been cogently reported to normalize blood glucose, cholesterol levels, hepatic lipid levels and to improve insulin signaling. By blocking the JNK pathway and the p38 MAPK pathway, Naringin reduces the secretion and transcription of IL-8, MCP-1 and macrophage inflammatory protein-1 alpha (MIP-1α), thereby reduces inflammation and liver fibrosis[53].

Curcumin (compound 24 in Table S1), a phenolic natural compound derived from turmeric, is known to have anti-inflammatory, antioxidant, anti-viral and anti-cancer activities. It is reported to reduce both acute inflammation and chronic inflammation contributing to its anti-fibrotic action. Curcumin decreases protein levels of TNF-α and MCP-1 in CCl_4-induced mouse fibrotic liver[54]. Curcumin also significantly reduces the level of inflammatory cytokines including TNF-α, IL-1β, IL-6 and cytokine-induced neutrophil chemoattractant-1, a rat homolog to human IL-8 in serum as well as in the liver of CCl_4-treated rats[55].

Corilagin (compound 25 in Table S1) is identified in several plants such as *Phyllanthus*. It is effective in hepatic protection with anti-inflammation, antioxidant, anti-HSV-1 encephalitis and anti-fibrosis effect. Corilagin reduces inflammation and reduces liver fibrosis caused by Schistosomiasis through inhibiting the expression of signaling molecules on IL-13 pathways[56].

Schisandrin B (Sch B, compound 26 in Table S1), the main active ingredient in *Schisandra Chinensis*, possesses diverse pharmacological activities such as antioxidative, anti-inflammatory, anti-tumor, and hepatoprotective properties. By activating the nuclear Nrf2-regulated antioxidant

pathway, Schisandrin B blocks the TGF-β/smad signaling pathway, therefore, it inhibits the activation of HSCs and reduces the levels of inflammatory factors IL-6, IL-1β and TNF-α to provide anti-fibrosis effect[57].

Breviscapine (compound 27 in Table S1) is a group of flavonoid glycosides isolated from Chinese herbs such as *Erigerin Breviscapus*. Breviscapine has been reported to have various biological activities including antioxidative, anti-cancer, anti-degenerative and anti-angiogenesis effects. Breviscapine reduces levels of ASL and ALT in serum. In addition, Breviscapine significantly reduces the levels of IL-1β, IL-6, TNF-α and MCP-1 by blocking TLR4 and NF-κB pathway, therefore, it reduces inflammation and significantly inhibits liver fibrosis[58].

Ellagic acid (EA) (compound 28 in Table S1) is a polyphenolic compound derived from plants found in a wide variety of nuts and fruits. It has been reported to possess various pharmacological actions including antioxidant, anti-mutagenic, anti-carcinogenic, anti-bacterial, anti-inflammatory, anti-diabetic, cardioprotective, and hepatoprotective activities. It is reported that EA reduces the accumulation of ROS, thereby reduces the release of inflammatory factors induced by ROS and the accumulation of collagen providing anti-fibrosis effect[59].

Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavone, compound 29 in Table S1) is a well-known flavonoid widely found in many plants and fruits including apples, red grapes, citrus fruits, tomato, onions and a number of berries. Quercetin is known to possess various biological and pharmacological activities including antioxidant, anti-viral, anti-inflammatory, anti-proliferative, and anti-fibrotic effects[60]. It has been found that quercetin reduces the expression of TNF-α, IL-1β, IL-6 and nitric oxide synthase 2 by regulating HMGB1 and TLR4 signaling pathways, therefore it provides anti-inflammatory response and anti-liver fibrosis effect[61].

The root of *Plumbago Zeylanica L.* has been used for centuries in traditional Indian and Chinese medicine for the treatment of various ailments. Plumbagin (5-hydroxy-2-methyl-1, 4 naphthoquinone, compound 30 in Table S1) is a quinonoid constituent that is found in the roots of Plumbago genus, and it exhibits diverse pharmacological effects[62]. Hyperlipidemic rabbits that received plumbagin exhibite definite regression of atheroma, reduced accumulation of cholesterol and triglycerides in the liver and aorta. Plumbagin also induces apoptosis and inhibits NF-κB and STAT3 signaling pathways, therefore reduces inflammation and liver fibrosis.

Artemisia annua (compound 31 in Table S1), a water-soluble hemisuccinate derivative of artemisinin extracted from the Chinese herb *Artemisia Annua*, is an effective anti-malarial drug. Many reports show that *Artemisia annua* exhibits anti-inflammatory and immune-modulatory effects in the treatment of inflammatory bowel disease. It also attenuats LPS-induced inflammatory responses in microglial BV2 cells and suppresses the inflammation of endotoxin-induced uveitis by inhibiting the production of inflammatory mediators[63]. It has been reported that it reduces the level of HMGB1 and the expression of inflammatory factor COX-2 to provide anti-inflammation and anti-fibrosis function[64]. By inhibiting the TLR4 and NF-κB signaling pathways, it reduces the levels of endotoxin, TNF-α, IL-6 and significantly reduces liver fibrosis[65].

Baicalin (5,6-dihydroxyflavone, compound 32 in Table S1), a bioactive flavonoid isolated from the root of *Scutellaria Baicalensis Georgi* (*Baical Skullcap Root*, *Scutellaria L.*, *Labiatae*), has many biological functions, including hepatoprotective effects[66]. It is reported that baicalin increases the level of PPARγ leading to the down-regulation of TGF-β signaling pathway and inhibition of hepatic stellate cells activation. Therefore, it reduces the release of inflammatory factor TNF-α providing the anti-fibrosis effect[67].

Astragalus Membranaceus is one of the most precious traditional Chinese medicinal plants with no obvious side effects. Astragaloside IV (compound 33 in Table S1) is the key ingredients isolated from *Astragalus Membranaceus*. The anti-fibrosis effect of Astragaloside IV has been widely confirmed. Its mechanism of action is related to the down-regulation of TGF-1, inhibition of collagen synthesis and proliferation in HSCs. In addition, Astragaloside IV also significantly inhibits the proliferation of PDGF associated with chronic liver inflammation[68].

Triptolide (compound 34 in Table S1) is a diterpene triepoxide extracted from *Tripterygium Wilfordii Hook F.* It is an effective immuno-suppressant and anti-inflammatory agent. It is observed that triptolide treatment significantly reduces liver fibrosis, collagen content, IL-6 and TNF-

α levels in the dimethylnitrosamine (DMN) treated liver fibrosis mouse model. The number of α-SMA and NF-κB positive cells have been decreased upon treatment with triptolide. Triptolide also inhibits TNF-α, TGF-β1-induced collagen deposition and secretion of α-SMA in HSC-T6 cells[69]. In addition, isolation of another component from *Tripterygium Wilfordii Hook F*, celastrol, is able to activate NLRP3 through the activation of inflammasome, thereby inhibiting the production of inflammatory factors such as IL-1β, TNF-α, *etc*. Therefore, celastrol may have potential activity to treat liver fibrosis through inflammatory inhibition[70].

Sophocarpine (compound 35 in Table S1) is the main pharmacologically active ingredient in the TCM *Radix Sophorae Subprostratae*. It has immuno-modulatory activity and can significantly reduce the content of inflammatory cytokines. It is found that Sophocarpine mainly reduces the degree of liver fibrosis by inhibiting TLR4 channels, reducing the levels of inflammatory cytokines such as TNF-α, TGF-β1 and IL-6. It also reduces the content of cyclin D1 and proliferating cell nuclear antigen (PCNA)[71].

Tanshinone IIA (compound 36 in Table S1) is one of the most pharmacological lipophilic active components isolated from *Savia miltiorrhiza*. It inhibits the formation of inflammasome by inhibition of nucleoside-binding oligomeric domain (NOD) receptor family protein 3 (NLRP3) under the NF-κB pathway[72]. It also reduces the release of cytokine IL-1β and inflammatory damage providing potential therapeutic method to treat liver fibrosis[73].

Ginsenoside-Rg1 (compound 37 in Table S1) is the most abundant content of *P. Notoginseng Saponins*, which can significantly inhibit cell proliferation, activation and ROS stimulated by platelet-derived growth-factor-BB (PDGF-BB). It also inhibits the expression of PDGF receptor β by reducing the activity of inflammatory signaling NF-κB. It possesses antioxidation and anti-fibrosis effects and has potential therapeutic value to treat liver fibrosis[74].

Berberine (BRB) (compound 38 in Table S1) is one of the active components in many Chinese herbal medicines, which can be used to treat steatohepatitis. It has been demonstrated that BRB inhibits inflammation by interfering with the activation of NLRP3 inflamosome pathway both *in vivo* and i*n vitro* based on interfering purinergic ligand-gated ion channel 7 receptor (P2X7) activation[75], providing prevention of early liver fibrosis.

Dioscin (compound 39 in Table S1), a steroidal saponin, is an active ingredient in some TCMs such as *Liuwei Dihuang Decoction* and *Di'ao Xinxue Kang*[76]. Dioscin has the ability to treat liver injury and provide anti-fibrosis activity. Studies show that diosgenin significantly up-regulates the level of silent information regulator 1 (Sirt1) and HO-1. Dioscin also reduces serum levels of alanine aminotran-sferase (ALT), aspartate transaminase (AST), and slows down acute liver injury[77]. It also inhibits the nuclear translocation of Nrf2 and suppresses the expression levels of forkhead box protein O1 (FOXO1) to inhibit oxidative stress. Diosgenin also significantly decreases the levels of inflammatory pathway NF-κB and the mRNA levels of TNF-α, IL-1β, and IL-6 to inhibit inflammatory response providing potential prevention of liver fibrosis[78].

Most of the above mentioned active natural compounds in the traditional Chinese herbal medicines have been reported to exhibit anti-inflammatory activity to prevent or treat liver fibrosis. Since the reported disease models are mostly acute liver injury model induced by chemicals such as CCl_4 or LPS, it is assumed that these natural ingredients are able to inhibit acute inflammation. However, in reality, these ingredients may also exhibit anti-chronic inflammatory activity. From the current studies, most of the active ingredients from TCMs to treat liver fibrosis inhibit inflammation by targeting at pathways including NF-κB, STAT3, TLR4, HMGB1, JNK, p38 and MAPK, *etc*. They decrease the inflammatory factors associated with liver fibrosis to relieve symptoms. Most of them are able to multi-target at several inflammatory factors rather than only one signal pathway, therefore providing better treatment through multi-function compared to the synthesized drugs.

3.2 Chinese herbal medicines to treat liver fibrosis through anti−inflammation

It is well known that TCMs have been traditionally used in the treatment of various diseases for thousands of years in Asian countries. With the continuous development and urgent need of medical research, TCM has gradually become a growing focus of worldwide medical research in order to get better therapeutic effect especially for chronic diseases such

as liver fibrosis. TCM is rich in alkaloids, stilbenes, phenanthrenes, benzofurans and some other compounds with good biological activities. In addition, small RNAs such as decoctosomes isolated from a variety of herbal decoctions were also found with potential anti-inflammatory and anti-fibrotic activity in recent years[79].

Amomum Xanthoides is a Chinese herb that improves thioacetamide (TAA) -induced liver fibrosis in rats by its antioxidant property and ability to inactivate hematopoietic stem cells by regulation of fibroblasts. It can be used to treat acute inflammation through reducing the infiltration of lymphocytes and phagocytes. The *in vivo* results also prove that *Amomum Xanthoides* reduces the activity of nitric oxide synthases (iNOS), TNF-α, TGF-β, PDGF-β and connective tissue growth factor (CTGF) [80] providing prevention of liver fibrosis.

Babao Dan is a traditional Chinese medicine that has been widely used as a supplement and alternative medicine to treat chronic liver disease including liver fibrosis. It is shown that *Babao Dan* can significantly protect the liver from diethylnitrosamine (DEN) induced liver damage by inhibition of early stage to late stage inflammation. It has also been found that *Babao Dan* can significantly inhibit LPS-induced HSCs activation by activating the TLR4/NF- κB pathway[81] therefore providing potential treatment of liver fibrosis .

Rabdosia Amethystoides (Benth) Hara extract is a traditional Chinese medicine with anti-bacterial, anti-tumor and anti-hepatitis effects. Its mechanism of action is related to the inhibition of oxidative stress and the release of inflammatory factors including TNF- α, INF- γ and IL-6. Its mechanism is also associated with down-regulation of TLR4 expression, inhibition of NF- κB activation, inhibition of IkBa kinase and p65 phosphorylation[82].

Centella Asiatica leaf extract has been shown to exhibit anti-inflammatory, anti-tumor activities and the ability to improve memory. Treatment using *Centella Asiatica* leaf extract significantly decreases the levels of inflammatory factors such as IL-1β, IL-2, IL-6, IL-10, TNF- α, IFN- γ and granulocyte/ macrophage colony-stimulating factor (GM-CSF) in rat liver damaged by dimethylnitrosamine (DMN), therefore providing anti-fibrosis effect. In addition, *Centella Asiatica* leaf extract significantly reduces the level of malondialdehyde (MDA) in rats, increases the activity of antioxidant enzymes including superoxide dismutase, glutathione peroxidase and catalase[83]. Therefore, it provides dual protection of liver fibrosis by dual-functional anti-inflammation and antioxidant activities.

Gynostemma Pentaphyllum is a commonly used Chinese medicine to treat hepatitis in Asia. It inhibits cell proliferation, the release of pro-inflammatory monocyte chemoattractant protein 1 (MCP-1) and the expression of type I pro-collagen[84]. Therefore, it provides effective treatment to inhibit the early stage of liver fibrosis.

Cortex Dictamni has been widely used to treat various inflammatory diseases, and it provides significant inhibition on the CCl_4-induced liver fibrosis in mice. It induces apoptosis in HSC-T6 cells and this process is associated with poly ADP ribose polymerase (PARP) pyrolysis and increased expression of caspase-3. *Cortex Dictamni* also activates JAK/STAT1 signaling in HSC-T6 cells, which provides a new treatment strategy for liver fibrosis[85].

Rundhanense is a precious Chinese herbal medicine. It is found that a polysaccharide DHP1A isolated from *Rundhanense* prevents hepatic inflammatory response caused by CCl_4 through anti-inflammatory effects. DHP1A reduces inflammation by decreasing the expression of inflammatory factors, chemokines, CD68 and p-IkBa induced by CCl_4[86].

Prunella Vulgaris has been widely used as medicine in Northeast Asian countries for the treatment of acute liver injury and infectious hepatitis. The protective effect of *Prunella Vulgaris* water extracts on CCl_4-induced liver fibrosis *in vivo* significantly decreases the level of TGF- β1 and Smad2. It also reduces ECM protein deposition, inflammatory stress, and HSCs activation providing prevention on liver fibrosis[87].

Dicliptera Chinensis is a traditional Chinese herb used in ancient China to treat liver diseases. The protective effect of *Dicliptera Chinensis* extracts on DMN-induced acute liver injury in rats is significant. It can reduce the activities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and increase the albumin content. In addition, it also reduces the content of TNF- α and IL-6 by blocking NF- κB signaling pathway [88].

The protective effect of *Indigofera Caerulea*

Roxb methanol extract (MIL) on liver protection *in vivo* has been studied showing that MIL reduces inflammation through antioxidant defense mechanisms. It prevents the activation of NF-κB and inhibits the release of pro-inflammatory cytokines TNF-α and IL-1β providing potential anti-fibrosis activity[89].

Glechoma Hederacea belongs to the mint family *Lamiaceae*. In the TCM, *Glechoma Hederacea* is frequently prescribed to patients suffering from cholelithiasis, dropsy, abscess, diabetes, inflammation and jaundice[90]. It has been reported that *Glechoma Hederacea* extracts inhibit HMGB1 and TLR4 signaling, block NF-κB activation, reduce inflammatory factor release and phagocytic activation, therefore alleviating bile duct ligation (BDL)-induced liver fibrosis[91].

Cordyceps Sinensis (Berk.) Sacc., a well-known tonic herb in TCM, is a highly valued fungus in China which can regulate the immune function. In recent years, cultured Mycelium Cordyceps Sinensis (CMCS) has been successfully developed and widely used as the alternative of natural *Cordyceps Sinensis (Berk.) Sacc*. CMCS significantly attenuates hepatic inflammation, decreases collagen deposition, and relieves levels of α-SMA in liver[92], but its signaling pathway has not been reported.

Solanum Nigrum L. is an herb that grows wildly and abundantly in open fields. It has been used to treat inflammation, edema, mastitis and hepatic cancer for a long time in TCM. A freshly prepared extract of the herb is effective in treating liver cirrhosis, and juice of the leaves alleviates pain in inflammation in kidney and bladder. It can also reduce serum ALT and AST, increase the levels of SOD and GSH in the blood, reduce the accumulation of ROS, thereby reducing the inflammatory response and alleviating liver fibrosis[93].

Bupleurum is a traditional Chinese medicine whose functions include antipyretic and analgesic, anti-inflammatory, anti-bacterial and immune enhancement. It is found that both *Bupleurum Marginatum Wall. Ex. DC* and *Bupleurum Chinense DC* have protective effects on acute liver injury induced by CCl_4 in mice through reducing the degree of HSC damage and relieving liver fibrosis. They both inhibit TGF-β synthesis and the expression of NF-κB, which in turn regulate TNF-α and TNF-β, granulocyte-macrophage colony stimulating factor (GM-CSF) and inflammatory factor IL-6[94]. It also increases the activity of antioxidant enzymes and inhibits lipid peroxidation, providing protection in liver fibrosis.

Our recent research has found out that *Bupleurum Marginatum Wall. Ex. DC* effectively alleviates the dimethylnitrosamine (DMN) induced liver damage and liver fibrosis in rats. The alcoholic extracts of *Bupleurum Marginatum Wall. Ex. DC* include triterpenoid saponin derivatives, flavonoids and lignin. Among them, saikosaponin C provides the best anti-fibrosis activities, followed by matairesinol monoglucoside and compound butyrolactone[95-96]. In addition, we have isolated several new saikosaponins from *Bupleurum Marginatum Wall. Ex. DC*, which have obvious inhibitory effects on HSC-T6 cell proliferation, providing potential anti-fibrosis role. However, whether their mechanism of action involved anti-inflammation pathway is still under research in our group.

3.3 Compound herbal formulae to treat liver fibrosis

Traditional Chinese medicines are famous for their specific formulae, which usually consist of several natural herbs having different or similar medicinal effects in one formula to provide better treatment. Natural herbs in one formula provide synergistic effect, therefore provide better treatment for liver fibrosis *via* multi-functions usually including antioxidative, anti-inflammation and anti-HSC proliferation pathways.

The combination of Glossy privet fruit and Ecliptae herbal formula can be used to treat liver disease by inhibiting the activity of KC in liver tissue in TMC. This formula can also reduce the content of cytokines related to liver damage, including TNF-α, IL-6 and TGF-β. It can also inhibit the production of mouse mononuclear macrophage leukemia cells RAW 264.7 induced by LPS. The possible protective mechanism may be to reduce the activation of KC and the expression of transaminase and pro-inflammatory cytokines[97], therefore providing inhibition of liver fibrosis.

YuGanLong is a formula composed of *Bupleurum*, *Scutellaria* and *Artemisiacapillaris Thunb*., which has been used to treat both the acute and chronic hepatitis and early cirrhosis of the liver providing potential to treat liver fibrosis. The results show that it reduces α-SMA in CCl_4-treated rats, up-regulated MMP-2, MMP-9 and Smad7. It also down-

regulates TIMP1, phosphorylation signal transduction p-Smad2, p-Smad3 and Smad4. YuGanLong also inhibits the increase of TGF-β1, TNF-α, IL-1β, IL-6, IL-4 and IL-17 A and promotes the expression of INF-γ. These results indicate that YuGanLong abolishes the balance between inflammatory factors IL-4, IL-17A and INF-γ by accelerating the degradation of extracellular matrix, blocking the TGF-β1/Smad signaling pathway, therefore alleviate CCl_4-induced liver fibrosis[98].

Compound Phyllanthus Urinsria consists of traditional Chinese medicines with hepatoprotective effects including *Underleaf Pearl*, *Radix Sophorae Flavescentis*, *Salvia Miltiorrhiza Bunge*, *Panaxus Rubensis*, and *Bupleurumchinensie DC*. It is mainly used for the treatment of chronic hepatitis B and liver fibrosis. It has been shown to alleviate liver pathological damage in mice with acute liver injury, reduce the activities of serum ALT and AST. It can also reduce the malondialdehyde (MDA) level, improve the superoxide dismutase (SOD) activity and glutathione GSH levels[99]. Therefore, compound Phyllanthus Urinsria can promote the metabolism of reactive oxygen species and peroxide, inhibit lipid peroxidation and provide liver protection.

Lycium Barbarum Polysaccharide is composed of six monosaccharides such as arabinose, glucose and galactose. It down-regulates pro-inflammatory factors TNF-α, iNOS, IL-1β and COX-2. It also decreases chemokines MCP-1, human macrophage inflammatory protein 2 (MIP-2) to reduce liver inflammation. Lycium Barbarum Polysaccharide can also significantly inhibit the expression of cytochrome P450 2E1, restore the expression level of antioxidant enzymes, reduce the level of nitric oxide and lipid peroxidation, and promote liver regeneration after CCl_4 injury. Its protective effect is partly achieved by down-regulating the activity of NF-κB. Therefore, Lycium Barbarum Polysaccharide can effectively reduce necrotic inflammation and oxidative stress caused by chemical toxins, and provide liver protection[100].

YiGuanJian is a traditional Chinese medicine formula composed of nine natural plants ingredients such as *Dihuang*, *Angelica* and *Astragalus*, *etc*. They provide synergistic effect on the treatment of liver injury. One of the main mechanisms of action is inhibition of TGF-β1, TGF-β receptors genes and protein expression[101]. It may also protect the liver from being damaged by lowering serum glutamate oxaloacetate transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels, as well as down-regulating the expression of α-SMA mRNA and protein to reduce the amount of activated HSCs[102].

Traditional Chinese formula YuZhangDan consists of *Schisandra*, *Polygonum Cuspidatum* and *Turmeric*. It provides anti-fibrosis effect by lowering ALT, AST, hyaluronate acid (HA), laminin (LN), type III procollagen peptide (PIII NP) and decreasing the expression of TGF-β1 and α-SMA in liver tissue[103].

The FuzhengHuayu (FZHY) formula, also called TCM 319, is a traditional Chinese prescription consisting of six traditional Chinese medicinal herbs. It can alleviate liver fibrosis induced by CCl_4 in rats. The anti-fibrosis effect is related to down regulating mRNA expression of TIMP-1 and PDGF-B which causes cell proliferation. In addition, it can also suppress protein expression of PDGF-Rβ and TGF-β1 by blocking the JNK and p38 MAPK signaling pathways[104-105].

A traditional formula Chunggan extract can be used to treat a variety of liver diseases including liver fibrosis. The corresponding mechanism is probably due to its antioxidative property to maintain the stability of glutathione and inhibit the production of ROS, thereby reducing the concentration of TGF-β and down-regulating TNF-α[106].

DaHuangZheChong pills are made up of *Rhei Radix Et Rhizoma*, *Persicae Semen*, *Paeoniae Radix Alba*, *Toxicodendri Resina*, *etc*, which have the function of promoting blood circulation, dredging meridians, relieving stress and improving liver function. It significantly reduces the amount of ALT, AST, HA, LN, type IV collagen and pro-collagen. It is also found to reverse the CCl_4-induced liver fibrosis in rats by down-regulating phosphorylation of p38 and extracellular signal-regulated kinase ERK, reducing the secretion of TNF-α and IL-13[107].

HV-P411 Complex is an herbal extract from the seeds of *Vitis Vinifera*, *Schisandra Chinensis* and *Taraxacumo Offificinale*. Its mechanism to prevent and treat liver fibrosis is to attenuate the transcription levels of TNF-α, IL-6 and COX-2, while increase the serum IL-10 level, heme oxygenase-1 protein production and their mRNA expression to counteract damage. HV-P411 Complex can restrain translocation of NF-κB and proto-oncogene c-Jun phosphorylation. In addition, it can also increase the content of GSH in

liver to reduce oxidative stress[108] providing multi-function to treat liver fibrosis.

Soshiho-tang is a traditional medicine in Northeast Asia described in Sang han-ron (150−219 AD in the Chinese Eastern Han Dynasty), an ancient Chinese medicine book. It is a mixture of seven natural herbs that can be used to treat chronic liver disease. It increases the content of natural killer cells (NK), interferon, IL-12, HO-1, Nrf2 and cytochrome p450 to exert chemopreventive effects. In addition, it also decreases the expression level of inflammatory mediator NF- κB and the adhesion molecule intercellular adhesion molecule-1 (ICAM-1). Its anti-fibrosis effect is through promoting the synthesis of liver protein, increasing liver plasma levels and microsomal enzyme activity to enhance the enzymatic antioxidant defense system. It can also inhibit lipid peroxidation and hepatic stellate cells' (HSCs) activity, decline the accumulation of ECM. It also inhibits the proliferation of liver cancer cells and inhibits the development of pre-neoplastic and tumor lesions in human and rats' livers[109] providing potential to treat liver fibrosis.

Jianpi Huoxue (JPHX), as a Chinese herbal formula, has been used to treat liver disease in China for many years. JPHX mainly consists of *Atractylodes Macrocephal* (Baishu), *Salvia Miltiorrhiza* (Danshen), *Rasux Paeonia Alba* (Baishao), *Rhizoma Alismatis* (Zexie), and *Fructus Schisandrae Chinensis* (Wuweizi). It has been found to strengthen the spleen, emolliate the liver, dispel dampness, dissolve stasis, and promote blood circulation[110] in Chinese medicine. JPHX can significantly reduce serum ALT and AST levels. In addition, JPHX has the potential to treat liver fibrosis by reducing the levels of TNF-α, collagen and matrix metalloproteinases[111].

KangXianRuanGan (KXRG) capsule is a classical formula containing *Artemisia Capillaries*, *Salvia Miltiorrhiza*, *Panax Notoginseng*, *Angelica Sinensis*, *Curcuma Zedoary*, *Parched Pangolin*, *Rhizoma Atractylodis Macrocephalae*, *Coix* seed and *Astragalus* membranaceus. It maintains the balance of TNF- α/IL-10, further reduces the inflammatory response and alleviates liver fibrosis[112].

From the aspect of traditional Chinese medicine, pathogenesis of liver fibrosis is a dynamic development process. The pathogenesis in different stages of liver fibrosis is different. Ideally the treatment should be focused on different pathways using various formulae. Formula containing natural medicines targeting at several pathways such as inhibiting longer generation of collagen, promoting collagen degradation, inhibiting the inflammation derived from liver fibrosis, reducing the oxidative stress, inhibiting the activation of HSCs will definitely provide better treatment rather than focusing on one pathway.

4 Perspective

Liver fibrosis occurs when chronic and continuous damage to liver accumulates. It is difficult to observe the symptoms in the early stage, but the onset chronic accumulation of liver fibrosis may result in liver cirrhosis or liver cancer eventually. Liver fibrosis can sometimes be reversed if it is identified and treated at the early stage. However, lack of effective non-invasive medical diagnostic methods makes it difficult to diagnose at the early stage. After months or years of continual damage, bands will form throughout the whole liver, destroying its internal structure and its regeneration and function. Due to the side effect or the non-specific treatment, the synthetic drugs could not reverse the symptoms of liver fibrosis very efficiently.

Due to the lack of effective early diagnostic techniques, the course of liver fibrosis usually has already entered to the chronic inflammatory stage by the time it is diagnosed. The traditional Chinese medicinal herbs are effective in slowing down the disease process or reversing liver fibrosis to some extent. Although the treatment of liver fibrosis from the perspective of TCM is mainly through the idea of activating blood and resolving stasis to reduce chronic inflammation, it is not particularly effective for the late stage liver fibrosis.

Active ingredients in the TCMs provide multiple mechanism of actions including antioxidant activities, the ability to reduce inflammation and anti-apoptosis through a variety of signaling pathways to regulate micro circulation, immune function and to improve liver function. A group of effective compounds with different mechanism of actions are the significant basis for TCM, especially Chinese herbal formulae including a large number of components working synergistically, but not focusing on one single signaling pathway. From the aspects of TCM, it is necessary to elaborate the active ingredients from

various natural herbals on the whole, otherwise it deviates from the theory of TCM.

Due to the differences and complexity in pathogenic mechanisms, the targets involved in different liver injury models studied in the lab are also very complex. How to find the most critical and common shared key targets in different cellular or animal models is a question that needs to be improved as well. It is necessary to establish more accurate cellular models or animal models that conform to the liver fibrosis condition in humans in order to examine the efficacy and mechanism of TCM more accurately.

At present, Chinese medicine treatment of liver injury especially fibrosis has been focused on discovery of active components and their targeted mechanisms. The synergistic effects of various active ingredients and the metabolites produced by different components needs to be further studied to provide insight on developing novel formulae as well as their new mechanisms. From the concept of TCM, the synergistic effect of different components and their metabolic targeting at several signaling pathways rather than one component working through single signaling pathway is more likely to be more effective. In order to clarify the mechanism of action more clearly for TCM in the future, synergistic effects should be studied thoroughly.

The molecular mechanism of liver fibrosis and the experimental study of TCM for the treatment will promote the development and clinical application of new Chinese medicine. However, there are more basic pre-clinical studies and fewer standardized clinical studies in terms of current research status. In the future research, it is necessary to pay more attention to the combination of basic research and clinical application. Combination of multiple therapies by integrating modern Chinese medicine and Western medicine will definitely open up a new research scope to develop safe, effective and inexpensive drugs to treat liver damage, especially in their early stage. Eradication of liver fibrosis in the early acute inflammatory phase can be achieved in the future with the improvement of early diagnostic techniques.

Supplementary material 20200183_Table S1. pdf is available at paper online (http:// www.pibb.ac.cn or http://www.cnki.net).

References

[1] Chen Y, Yu L, Wei Y, *et al*. D-ribose increases triglyceride *via* upregulation of DGAT in the liver. Sci China Life Sci, 2019, **62**(6): 858-861

[2] Meng X, Li Y, Li S, *et al*. Natural products for prevention and treatment of chemical-induced liver injuries. Comprehensive Reviews in Food Science and Food Safety, 2018, **17**(2): 472-495

[3] Xu R, Zhang Z, Wang F. Liver fibrosis: mechanisms of immune-mediated liver injury. Cell Mol Immunol, 2018, **9**(4): 296-301

[4] Wang S, Pacher P, De Lisle R C, *et al*. A mechanistic review of cell death in alcohol-induced liver injury. Alcohol Clin Exp Res, 2016, **40**(6): 1215-1223

[5] Tsuchida T, Friedman S T. Mechanisms of hepatic stellate cell activation. Natre Reviews Gastroenterology & Hepatology, 2017, **14**(7): 397-411

[6] Zhou Y, Wang X, Fan S, *et al*. A lumbrokinase isozyme targets hepatitis B e-antigen. Sci China Life Sci, 2018, **61**(12): 1596-1598

[7] Chen W J, Wu Y, Zhao X, *et al*. Screening the anti-gout traditional herbs from TCM using an *in vitro* method. Chin Chem Lett, 2016, **27** (11): 1701-1707

[8] 段桂姣, 蒋锐沅, 王振常 . 中药抗肝纤维化作用机制的研究进展 . 中医药导报, 2020, **26**(5): 113-117
Duan G J, Jiang R Y, Wang Z C. Guiding Journal of Traditional Chinese Medicine and Pharmacy, 2020, **26** (5): 113-117

[9] Bataller R, Brenner D A. Liver fibrosis. J Clin Invest., 2005, **115** (2): 209-218

[10] Gabele E, Brenner D A, Rippe R A. Liver fibrosis: signals leading to the amplification of the fibrogenic hepatic stellate cell. Front Biosci, 2003, **8**: d69-77

[11] Foglia B, Cannito S, Bocca C, *et al*. ERK pathway in activated, myofibroblast-like, hepatic stellate cells: a critical signaling crossroad sustaining liver fibrosis. Int J Mol Sci, 2019, **20** (11): 2700-2721

[12] She L L, Xu D, Wang Z X, *et al*. Curcumin inhibits hepatic stellate cell activation *via* suppression of succinate-associated HIF-1 alpha induction. Mol Cell Endocrinol, 2018, **476**: 129-138

[13] Schuppan D, Ashfaq-Khan M, Yang A T, *et al*. Liver fibrosis: direct antifibrotic agents and targeted therapies. Matrix Biology, 2018, **68-69**: 435-451

[14] Sherwood E R, Toliver-Kinsky T. Mechanisms of the inflammatory response. Best Pract Res Clin Anaesthesiol, 2004, **18** (3): 385-405

[15] Liew F Y. The role of innate cytokines in inflammatory response. Immuno Lett, 2003, **85**(2): 131-134

[16] Maleki S J, Crespo J F, Cabanillas B. Anti-inflammatory effects of flavonoids. Food Chem, 2019, **299**: 125124

[17] Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci, 2014, **69 Suppl1**: S4-S9

[18] Armutcu F. Organ crosstalk: the potent roles of inflammation and fibrotic changes in the course of organ interactions. Inflamm Res, 2019, **68** (10): 825-839

[19] Liu T, Zhang L Y, Joo D, *et al*. NF-kappa B signaling in inflammation. Signal Transduct Target Ther, 2017, **2**: 17023

[20] Kwak B J, Choi H J, Kim O H, *et al*. The role of phospho-c-Jun N-Terminal kinase expression on hepatocyte necrosis and autophagy in the cholestatic liver. J Surg Res, 2019, **241**: 254-263

[21] Avalle L, Camporeale A, Morciano G, *et al*. STAT3 localizes to the ER, acting as a gatekeeper for ER- mitochondrion Ca^{2+} fluxes and apoptotic responses. Cell Death Differ, 2019, **26** (5): 932-942

[22] Ramos-Tovar E, Muriel P. Free radicals, antioxidants, nuclear factor-E2-related factor-2 and liver damage. J App Toxicol, 2019, **40**(1): 151-168

[23] Peng J H. The pharmacological targets and clinical evidence of natural products with anti-hepatic inflammatory properties. Front Pharmacol, 2018, **9**: 455

[24] Weston C J, Zimmermann H W, Adams D H. The role of myeloid-derived cells in the progression of liver disease. Front Immuno, 2019, **10**: 893

[25] Tsuchida T, Friedman S L. Mechanisms of hepatic stellate cell activation. Nat Rev Gastro Hepat, 2017, **14** (7): 397-411

[26] Willett C, Rae J C, Goyak K O, *et al*. Pathway-based toxicity: history, current approaches and liver fibrosis and steatosis as prototypes. Altex-Altern Anim Ex, 2014, **31** (4): 407-421

[27] Yang J J, Tao H, Li J. Hedgehog signaling pathway as key player in liver fibrosis: new insights and perspectives. Expert Opin Ther Tar, 2014, **18** (9): 1011-1021

[28] Malik A, Kanneganti T D. Function and regulation of IL-1alpha in inflammatory diseases and cancer. Immunol Rev, 2018, **281** (1): 124-137

[29] Koyama Y, Brenner D A. Liver inflammation and fibrosis. J Clin Invest, 2017, **127** (1): 55-64

[30] 杨湖 . 炎症中医辨治管见 . 江西中医药, 1996, **S1**: 10-11
Yang H. Jiangxi Journal of Traditional Chinese Medicine, 1996, **S1**: 10-11

[31] Chen P J, Ko I L, Lee C L, *et al*. Targeting allosteric site of AKT by 5,7-dimethoxy-1,4-phenanthrenequinone suppresses neutrophilic inflammation. Ebiomedicine, 2019, **40**: 528-540

[32] Itharat A, Hiransai P. Dioscoreanone suppresses LPS-induced nitric oxide production and inflammatory cytokine expression in RAW 264.7 macrophages by NF-kappa B and ERK1/2 signaling transduction. J Cell Biochem, 2012, **113** (11): 3427-3435

[33] Lim J S, Hahn D, Gu M J, *et al*. Anti-inflammatory and antioxidant effects of 2, 7-dihydroxy-4, 6-dimethoxy phenanthrene isolated from Dioscorea batatas Decne. Appl Biol Chem, 2019, **62**(1): 1-9

[34] Lee W, Jeong S Y, Gu M J, *et al*. Inhibitory effects of compounds isolated from Dioscorea batatas Decne peel on particulate matter-induced pulmonary injury in mice. J Toxicol Env Heal A, 2019, **82** (12): 727-740

[35] Semenok D, Medvedev J, Giassafaki L P, *et al*. 4, 5-Diaryl 3(2H) furanones: anti-inflammatory activity and influence on cancer growth. Molecules, 2019, **24** (9): 1751-1775

[36] Li J Y, Kuang M T, Yang L, *et al*. Stilbenes with anti-inflammatory and cytotoxic activity from the rhizomes of Bletilla ochracea Schltr. Fitoterapia, 2018, **127**: 74-80

[37] Kim J H, Oh S Y, Han S B, *et al*. Anti-inflammatory effects of Dendrobium nobile derived phenanthrenes in LPS-stimulated murine macrophages. Arch Pharm Res, 2015, **38** (6): 1117-1126

[38] Lu Y, Jin M H, Park S J, *et al*. Batatasin I, a naturally occurring phenanthrene derivative, isolated from tuberous roots of Dioscorea batatas suppresses eicosanoids generation and degranulation in bone marrow derived-mast cells. Biol Pharm Bull, 2011, **34** (7): 1021-1025

[39] Datla P, Kalluri M D, Basha K, *et al*. 9, 10-Dihydro-2, 5-dimethoxyphenanthrene-1, 7-diol, from Eulophia ochreata, inhibits inflammatory signalling mediated by Toll-like receptors. Brit J Pharmacol, 2010, **160** (5): 1158-1170

[40] Di Pascoli M, Divi M, Rodriguez-Vilarrupla A, *et al*. Resveratrol improves intrahepatic endothelial dysfunction and reduces hepatic fibrosis and portal pressure in cirrhotic rats. J Hepatol, 2013, **58** (5): 904-910

[41] 刘烨, 彭雅琦, 邹艳, 等 . 负载白藜芦醇的玉米醇溶蛋白-果胶纳米粒抗氧化活性及其对急性炎症小鼠的抗炎作用 . 现代食品科技, 2020, **36**(5): 7-13
Liu Y, Peng Y Q, Zou Y, *et al*. Modern Food Science and Technology, 2020, **36**(5): 7-13

[42] 苗玉连, 武传龙, 刘金波, 等 . 白藜芦醇对高脂饮食去卵巢肥胖大鼠脑组织炎症反应及海马 Aβ_(1-42)水平的影响 . 山东大学学报(医学版), 2013, **51**(8): 17-21
Miao Y L, Wu C L, Liu J B, *et al*. Journal of Shandong University (Health Sciences), 2013, **51** (8): 17-21

[43] Zurier R B, Burstein S H. Cannabinoids, inflammation, and fibrosis. Faseb J, 2016, **30** (11): 3682-3689

[44] Zhao S S, Li N R, Zhen Y Z, *et al*. Protective effect of gastrodin on bile duct ligation-induced hepatic fibrosis in rats. Food Chem Toxicol, 2015, **86**: 202-207

[45] Yang P, Han Y, Gui L, *et al*. Gastrodin attenuation of the inflammatory response in H9c2 cardiomyocytes involves inhibition of NF-kappa B and MAPKs activation *via* the phosphatidylinositol 3-kinase signaling. Biochem Pharmacol, 2013, **85** (8): 1124-1133

[46] Ligresti A, Villano R, Allara M, *et al*. Kavalactones and the endocannabinoid system: the plant-derived yangonin is a novel CB1 receptor ligand. Pharmacol Res, 2012, **66** (2): 163-169

[47] Dong R, Yang X, Wang C, *et al*. Yangonin protects against non-alcoholic fatty liver disease through farnesoid X receptor. Phytomedicine, 2019, **53**: 134-142

[48] Wang X, Ikejima K, Kon K, *et al*. Ursolic acid ameliorates hepatic fibrosis in the rat by specific induction of apoptosis in hepatic stellate cells. J Hepatol, 2011, **55** (2): 379-387

[49] Kimura M, Inoue H, Hirabayashi K, *et al*. Glycyrrhizin and some analogues induce growth of primary cultured adult rat hepatocytes via epidermal growth factor receptors. Eur J Pharmacol, 2001, **431** (2): 151-161

[50] Li X J Y, Sun R, Liu R P. Natural products in licorice for the therapy of liver diseases: progress and future opportunities. Pharmacol Res, 2019, **144**: 210-226

[51] Su S, Wu J, Gong T, *et al*. Inhibition of high mobility group box 1-toll-like receptor-4 signaling by glycyrrhizin contributes to the attenuation of cold ischemic injury of liver in a rat model. Transpl

P, 2016, **48** (1): 191-198

[52] Tripoli E, La Guardia M, Giammanco S, *et al*. Citrus flavonoids: molecular structure, biological activity and nutritional properties: a review. Food Chem, 2007, **104** (2): 466-479

[53] Zhou C Y, Lai Y L, Huang P, *et al*. Naringin attenuates alcoholic liver injury by reducing lipid accumulation and oxidative stress. Life Sci, 2019, **216**: 305-312

[54] Chen D Q, Feng Y L, Cao G, *et al*. Natural products as a source for antifibrosis therapy. Trends Pharmacol Sci, 2018, **39** (11): 937-952

[55] Bae M, Park Y K, Lee J Y. Food components with antifibrotic activity and implications in prevention of liver disease. J Nutr Biochem, 2018, **55**: 1-11

[56] Li H R, Li G, Li M, *et al*. Corilagin ameliorates schistosomiasis hepatic fibrosis through regulating IL-13 associated signal pathway *in vitro* and *in vivo*. Parasitology, 2016, **143** (12): 1629-1638

[57] Chen Q, Zhang H, Cao Y, *et al*. Schisandrin B attenuates CCl_4-induced liver fibrosis in rats by regulation of Nrf2-ARE and TGF-beta/Smad signaling pathways. Drug Des Devel Ther, 2017, **11**: 2179-2191

[58] Hu Y X, Yu C H, Wu F, *et al*. Antihepatofibrotic effects of aqueous extract of prunella vulgaris on carbon tetrachloride-induced hepatic fibrosis in rats. Planta Medica, 2016, **82** (1-2): 97-105

[59] Afifi N A, Ibrahim M A, Galal M K. Hepatoprotective influence of quercetin and ellagic acid on thioacetamide-induced hepatotoxicity in rats. Can J Physiol Pharmacol, 2018, **96** (6): 624-629

[60] Kim Y J, Park W. Anti-inflammatory effect of quercetin on RAW 264.7 mouse macrophages induced with polyinosinic-polycytidylic acid. Molecules, 2016, **21** (4): 450-459

[61] Li X, Jin Q W, Yao Q Y, *et al*. The flavonoid quercetin ameliorates liver inflammation and fibrosis by regulating hepatic macrophages activation and polarization in mice. Front Pharmacol, 2018, **9**: 72

[62] Parimala R, Sachdanandam P. Effect of plumbagin on some glucose metabolizing enzymes studied in rats in experimental hepatoma. Mol Cell Biochem, 1993, **125** (1): 59-63

[63] Lee I S, Ryu D K, Lim J, *et al*. Artesunate activates Nrf2 pathway-driven anti-inflammatory potential through ERK signaling in microglial BV2 cells. Neurosci Lett, 2012, **509** (1): 17-21

[64] Kim K E, Ko K H, Heo R W, *et al*. Artemisia annua leaf extract attenuates hepatic steatosis and inflammation in high-fat diet-fed mice. J Med Food, 2016, **19** (3): 290-299

[65] Lai L N, Chen Y X, Tian X X, *et al*. Artesunate alleviates hepatic fibrosis induced by multiple pathogenic factors and inflammation through the inhibition of LPS/TLR4/NF-kappa B signaling pathway in rats. Eur J Pharmacol, 2015, **765**: 234-241

[66] Liu L L, Gong L K, Wang H, *et al*. Baicalin protects mouse from Concanavalin a-induced liver injury through inhibition of cytokine production and hepatocyte apoptosis. Liver Int, 2007, **27** (4): 582-591

[67] Qiao H X, Han H C, Hong D S, *et al*. Protective effects of baicalin on carbon tetrachloride induced liver injury by activating PPAR gamma and inhibiting TGF beta 1. Pharm Biol, 2011, **49** (1): 38-45

[68] Liu H, Wei W, Sun W Y, *et al*. Protective effects of astragaloside IV on porcine-serum-induced hepatic fibrosis in rats and *in vitro* effects on hepatic stellate cells. J Ethnopharmacol, 2009, **122** (3): 502-508

[69] Chong L W, Hsu Y C, Chiu Y T, *et al*. Antifibrotic effects of triptolide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats. Phytother Res, 2011, **25** (7): 990-999

[70] Sang X S, Chen Y H, Chen W, *et al*. Celastrol specifically inhibits the activation of NLRP3 inflammasome. Sci China Life Sci, 2018, **61**: 355-357

[71] Sang X X, Wang R L, Zhang C E, *et al*. Sophocarpine protects mice from ConA-induced hepatitis *via* inhibition of the IFN-Gamma/STAT1 Pathway. Front Pharmacol, 2017, **8**: 140

[72] 武鹏宇, 戴立里, 唐静, 等. 丹参素对肝星状细胞增殖、活化及TGFβ/BMP受体表达的影响. 重庆医科大学学报, 2010, **35**(9):1344-1347
Wu P Y, Dai L L, Tang J, *et al*. Journal of Chongqing Medical University, 2010, **35** (9): 1344-1347

[73] Chen T Y, Qin S Y, Dai Y. Tanshinone IIA ameliorates acute lung injury by inhibition of the NLRP3 inflammasome. Arch Biol Sci, 2019, **71** (2): 315-320

[74] Geng J W, Peng W, Huang Y G, *et al*. Ginsenoside-Rg1 from Panax notoginseng prevents hepatic fibrosis induced by thioacetamide in rats. Eur J Pharmacol, 2010, **634** (1-3): 162-169

[75] Vivoli E, Cappon A, Milani S, *et al*. NLRP3 inflammasome as a target of berberine in experimental murine liver injury: interference with P2X(7) signalling. Clin Sci, 2016, **130** (20): 1793-1806

[76] Cheng X W, Su X Q, Chen X H, *et al*. Biological ingredient analysis of traditional Chinese medicine preparation based on high-throughput sequencing: the story for Liuwei Dihuang Wan. Sci Rep, 2014, **4**: 5147

[77] Tao X F, Yin L H, Xu L N, *et al*. Dioscin: a diverse acting natural compound with therapeutic potential in metabolic diseases, cancer, inflammation and infections. Pharmacol Res, 2018, **137**: 259-269

[78] Zhang X L, Han X, Yin L H, *et al*. Potent effects of dioscin against liver fibrosis. Sci Rep, 2015, **5**: 9713

[79] Li X, Liang Z, Du J, *et al*. Herbal decoctosome is a novel form of medicine. Sci China Life Sci, 2019, **62**(3): 333-348

[80] Wang J H, Shin J W, Choi M K, *et al*. An herbal fruit, Amomum xanthoides, ameliorates thioacetamide-induced hepatic fibrosis in rat *via* antioxidative system. J Ethnopharmacol, 2011, **135** (2): 344-350

[81] Liang L, Yang X, Yu Y, *et al*. Babao Dan attenuates hepatic fibrosis by inhibiting hepatic stellate cells activation and proliferation *via* TLR4 signaling pathway. Oncotarget, 2016, **7** (50): 82554-82566

[82] Zhai K F, Duan H, Cao W G, *et al*. Protective effect of Rabdosia amethystoides (Benth) Hara extract on acute liver injury induced by Concanavalin A in mice through inhibition of TLR4-NF-kappa B signaling pathway. J Pharmacol Sci, 2016, **130** (2): 94-100

[83] Choi M J, Zheng H M, Kim J M, *et al*. Protective effects of Centella asiatica leaf extract on dimethylnitrosamine-induced liver injury in rats. Mol Med Rep, 2016, **14** (5): 4521-4528

[84] Chen M H, Wang Q F, Chen L G, *et al*. The inhibitory effect of

Gynostemma pentaphyllum on MCP-1 and type I procollagen expression in rat hepatic stellate cells. J Ethnopharmacol, 2009, **126** (1): 42-49

[85] Wu X X, Wu L M, Fan J J, *et al*. Cortex Dictamni extract induces apoptosis of activated hepatic stellate cells *via* STAT1 and attenuates liver fibrosis in mice. J Ethnopharmacol, 2011, **135** (1): 173-178

[86] Tian C C, Zha X Q, Luo J P. A polysaccharide from Dendrobium huoshanense prevents hepatic inflammatory response caused by carbon tetrachloride. Biotechnol Biotec Eq, 2015, **29** (1): 132-138

[87] Hu Y X, Yu C H, Wu F, *et al*. Antihepatofibrotic effects of aqueous extract of prunella vulgaris on carbon tetrachloride-induced hepatic fibrosis in rats. Planta Med, 2016, **82** (1-2): 97-105

[88] Zhang K F, Gao Y, Zhong M L, *et al*. Hepatoprotective effects of Dicliptera chinensis polysaccharides on dimethylnitrosamine-induced hepatic fibrosis rats and its underlying mechanism. J Ethnopharmacol, 2016, **179**: 38-44

[89] Ponmari G, Annamalai A, Gopalakrishnan V K, *et al*. NF-kappa B activation and proinflammatory cytokines mediated protective effect of Indigofera caerulea Roxb. on CCl_4 induced liver damage in rats. Int Immunopharmacol, 2014, **23** (2): 672-680

[90] Vogl S, Picker P, Mihaly-Bison J, *et al*. Ethnopharmacological *in vitro* studies on Austria's folk medicine-an unexplored lore *in vitro* anti-inflammatory activities of 71 Austrian traditional herbal drugs. J Ethnopharmacol, 2013, **149** (3): 750-771

[91] Wang Y Y, Lin S Y, Chen W Y, *et al*. Glechoma hederacea extracts attenuate cholestatic liver injury in a bile duct-ligated rat model. J Ethnopharmacol, 2017, **204**: 58-66

[92] Peng Y, Tao Y Y, Wang Q L, *et al*. Ergosterol is the active compound of cultured mycelium cordyceps sinensis on antiliver fibrosis. Evid Based Complment Alternat Med, 2014, **2014**: 537234

[93] Lin H M, Tseng H C, Wang C J, *et al*. Hepatoprotective effects of Solanum nigrum Linn extract against CCl_4-iduced oxidative damage in rats. Chem-Biol Interact, 2008, **171** (3): 283-293

[94] 杜婷, 杜士明, 王刚, 等. 竹叶柴胡与北柴胡的抗炎保肝作用比较. 医药导报, 2014, **33**(9): 1144-1149
Du T, Du S M, Wang G, *et al*. Herald of Medicine, 2014, **33**(9): 1144-1149

[95] Liu X J, Shi Y, Jia S H, *et al*. Six new C-21 steroidal glycosides from Dregea sinensis Hemsl. J Asian Nat Prod Res, 2017, **19** (8): 745-753

[96] Liu X J, Dai R J, Ke M, *et al*. Differential proteomic analysis of dimethylnitrosamine (DMN) -induced liver fibrosis. Proteomics, 2017, **17** (22). doi:10.1002/pmic.201700267

[97] Zhao L J, Wang Q, Zhu X Q, *et al*. Liver-protecting effects of extracts from Glossy privet fruit and Ecliptae herba formula in mice through suppression of Kupffer cells activation. Food Agr Immunol, 2019, **30** (1): 222-235

[98] Xia Y, Yu B, Ma C Z, *et al*. Yu Gan Long reduces rat liver fibrosis by blocking TGF-beta 1/Smad pathway and modulating the immunity. Biomed Pharmacother, 2018, **106**: 1332-1338

[99] 陈斯泰, 何素, 李常青. 叶下珠复方II号对四氯化碳致小鼠急性肝损伤的保护作用. 中国热带医学, 2016, **16**(8): 766-769
Chen S T, He S, Li C Q. China Tropical Medicine, 2016, **16** (8): 766-769

[100] Xiao J, Liong E C, Ching Y P, *et al*. Tipoe, G. L.,Lycium barbarum polysaccharides protect mice liver from carbon tetrachloride-induced oxidative stress and necroinflammation. J Ethnopharmacol, 2012, **139** (2): 462-470

[101] 房澍名, 姚冬梅, 王军民, 等. 益肝康拆方药物血清对肝星状细胞 TGF-β1 及受体影响的研究. 中药药理与临床, 2009, **25**(2): 105-107
Fang Z M, Yao D M, Wang J M, *et al*. Pharmacology and Clinics of Chinese Materia Medica, 2009, **25** (2): 105-107

[102] Lin H J, Chen J Y, Lin C F, *et al*. Hepatoprotective effects of Yi Guan Jian, an herbal medicine, in rats with dimethylnitrosamine-induced liver fibrosis. J Ethnopharmacol, 2011, **134** (3): 953-960

[103] Zhou Y X, Chen J, Li J P, *et al*. Chinese medicinal herbs in treating model rats with hepatic fibrosis. Afr J Tradit Complem, 2010, **7** (2): 104-108

[104] Cheung K F, Ye D W, Yang Z F, *et al*. Therapeutic efficacy of traditional Chinese medicine 319 recipe on hepatic fibrosis induced by carbon tetrachloride in rats. J Ethnopharmacol, 2009, **124** (1): 142-150

[105] Dong S, Cai F F, Chen Q L, *et al*. Chinese herbal formula Fuzheng Huayu alleviates CCl_4-induced liver fibrosis in rats: a transcriptomic and proteomic analysis. Acta Pharmacol Sin, 2018, **39** (6): 930-941

[106] Kwak K G, Wang J H, Shin J W, *et al*. A traditional formula, Chunggan extract, attenuates thioacetamide-induced hepatofibrosis *via* GSH system in rats. Hum Exp Toxicol, 2011, **30** (9): 1322-1332

[107] Cai H B, Sun X G, Liu Z F, *et al*. Effects of dahuangzhechong pills on cytokines and mitogen activated protein kinase activation in rats with hepatic fibrosis. J Ethnopharmacol, 2010, **132** (1): 157-164

[108] Kang J W, Kim S J, Kim H Y, *et al*. Protective effects of HV-P411 complex against D-galactosamine-induced hepatotoxicity in Rats. Am J Chinese Med, 2012, **40** (3): 467-480

[109] Lee J K, Kim J H, Shin H K. Therapeutic effects of the oriental herbal medicine Sho-saiko-to on liver cirrhosis and carcinoma. Hepatol Res, 2011, **41** (9): 825-837

[110] Wang L L, Ma R F, Liu C Y, *et al*. Salvia miltiorrhiza: a potential red light to the development of cardiovascular diseases. Curr Pharm Design, 2017, **23** (7): 1077-1097

[111] Feng Y, Chen Y, Yang B, *et al*. Hepatoprotective effect of Jianpi Huoxue Formula on nonalcoholic fatty liver disease induced by methionine-choline-deficient diet in rat. Biomed Res Int, 2019: 7465272

[112] Liu L M, Zhou Y, Dai D, *et al*. Protective effects of Kangxian ruangan capsule against nonalcoholic fatty liver disease fibrosis in rats induced by MCD diet. Biomed Pharmacother, 2018, **108**: 424-434

中医药的抗炎机制在治疗肝纤维化中的作用*

李　博[1,2)**]　冯文韬[1)]　李静祎[1)]　李天媚[1)]　曹艳璐[1)]
吕　芳[1)]　戴荣继[1)**]　邓玉林[1)**]

([1)] 北京理工大学生命学院生物医药成分分离与分析北京市重点实验室，北京 100081；
[2)] 北京理工大学前沿交叉科学研究院，北京 100081）

摘要　肝脏是人体腹腔内最大的实体器官，对维持机体的基本生理功能起着至关重要的作用. 肝脏疾病是威胁人类健康的常见病多发病. 全球约有10%人口受到不同程度肝脏疾病的危害，其中肝纤维化往往成为这些疾病的晚期病理特征. 由于肝纤维化的发病机制复杂，尚无有效的合成类药物能够治疗肝纤维化. 中药治疗肝纤维化具有多靶点和副作用小的优势. 本文综述了肝纤维化的病理特征与诱发炎症的关系，讨论了中药治疗肝纤维化的单味中药、传统配方及其化学活性成分的抗炎症机制.

关键词　肝纤维化，传统中医药，抗炎治疗，作用机制
中图分类号　R28，Q947　　**DOI**：10.16476/j.pibb.2020.0183

* 北京理工大学青年教师学术启动计划资助项目.
** 通讯联系人.
李博. Tel：010-68913188，E-mail：boli@bit.edu.cn
戴荣继. Tel：010-68913310，E-mail：dairongji@bit.edu.cn
邓玉林. Tel：010-68914907，E-mail：deng@bit.edu.cn
收稿日期：2020-06-01，接受日期：2020-06-09