

Progress on traditional Chinese medicine in improving hepatic fibrosis through inhibiting oxidative stress

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Abstract

Hepatic fibrosis is a common pathological process that occurs in the development of various chronic liver diseases into cirrhosis and liver cancer, characterized by excessive deposition of the extracellular matrix. In the past, hepatic fibrosis was thought to be a static and irreversible pathological process. In recent years, with the rapid development of molecular biology and the continuous in-depth study of the liver at the microscopic level, more and more evidence has shown that hepatic fibrosis is a dynamic and reversible process. Therefore, it is particularly important to find an effective, simple, and inexpensive method for its prevention and treatment. Traditional Chinese medicine (TCM) occupies an important position in the treatment of hepatic fibrosis due to its advantages of low adverse reactions, low cost, and multi-target effectiveness. A large number of research results have shown that TCM monomers, single herbal extracts, and TCM formulas play important roles in the prevention and treatment of hepatic fibrosis. Oxidative stress (OS) is one of the key factors in the occurrence and development of hepatic fibrosis. Therefore, this article reviews the progress in the understanding of the mechanisms of TCM monomers, single herbal extracts, and TCM formulas in preventing and treating hepatic fibrosis by inhibiting OS in recent years, in order to provide a reference and basis for drug therapy of hepatic fibrosis.

Key Words: Hepatic fibrosis; Oxidative stress; Traditional Chinese medicine monomer; Single herbal extract; Traditional Chinese medicine formula

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Core Tip: Hepatic fibrosis is a common pathological process that occurs in the development of various chronic liver diseases into cirrhosis and liver cancer, characterized by excessive deposition of the extracellular matrix. This article reviews the progress in the understanding of the mechanisms of traditional Chinese medicine (TCM) monomers, single herbal extracts, and TCM formulas in preventing and treating hepatic fibrosis by inhibiting oxidative stress in recent years, in order to provide a reference and basis for drug therapy of hepatic fibrosis.

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INTRODUCTION

The prevalence of hepatic fibrosis ranges from 2% to 19%, and it remains a major cause of morbidity and mortality worldwide[1,2]. It leads to notorious complications such as ascites, portal hypertension, hepatic encephalopathy, and liver failure, and increases the risk of hepatocellular carcinoma, posing a heavy burden on individuals, society, and healthcare systems[3,4]. Currently, Western medical treatments for hepatic fibrosis include antiviral drugs, corticosteroids, hepatoprotective drugs, and liver support, but they have low efficacy rates, significant resistance, and side effects [5]. Traditional Chinese medicine (TCM), as a unique medical approach in China, has better safety and effectiveness and is widely used to treat hepatic fibrosis[6]. Continuous oxidative stress (OS) in the liver can induce biological changes in hepatocytes, leading to fibrotic changes in the liver[7]. Based on this, experts and scholars have conducted relevant experimental studies to demonstrate that TCM monomers, single herbal extracts, and TCM formulas can significantly improve the condition of hepatic fibrosis by regulating OS. Therefore, this article reviews the progress in the the understanding of the mechanisms of TCM in preventing and treating hepatic fibrosis by using OS as a starting point to provide references for the clinical treatment of hepatic fibrosis with TCM.

MECHANISMS OF HEPATIC FIBROSIS

Hepatic fibrosis is a chronic wound healing response to cellular damage and inflammation caused by increased synthesis and deposition of extracellular matrix (ECM) components and decreased or unbalanced ECM degradation (Figure 1)[8,9]. Various etiologies such as alcohol abuse, viral hepatitis infection, genetic abnormalities, non-alcoholic fatty liver disease, autoimmune disorders, and other non-infectious diseases can cause continuous wound healing response and liver injury, leading to hepatic fibrosis[10]. The main mechanism of hepatic fibrosis is believed to be the activation of myofibroblast precursor cells, which leads to an increase in ECM deposition surrounding the sinusoidal cell layer in the Disse space[11, 12]. ECM increase is the main feature of hepatic fibrosis, and the ECM is composed of five types of substances, collagen, non-collagenous proteins, elastic fibers, proteoglycans, and glycosaminoglycans. It is mainly divided into basement membrane and interstitial matrix according to its distribution site[13]. In human patients and rodent models of liver disease, fibrotic livers contain multiple types of collagen (types I, III, and V), non-fibrillar collagens (IV and VI), and glycosaminoglycans and proteoglycans (such as fibronectin, tenascin, laminin, basement membrane proteoglycans, decorin, biglycan, and fibrillin)[11].

In addition, hepatic stellate cells (HSCs) (Ito cells and lipocytes), portal-resident fibroblasts (portal or central veins), epithelial cells undergoing epithelial-to-mesenchymal transition, bone marrow-derived fibroblasts, vascular smooth muscle cells, and sinusoidal peri-hematopoietic stem cells are the main cell types that produce the ECM during hepatic fibrosis[14]. In human patients, HSCs constitute 5%-8% of the total liver cells involved in growth, differentiation, and regeneration. They are not only the main source of myofibroblasts but also the main cell type leading to hepatic fibrosis [15]. Portal fibroblasts are thought to play an important role in fibrosis in cholestatic liver disease[16,17]. The static HSC to myofibroblast differentiation is a multi-step process involving reactive oxygen species (ROS), cytokines, chemokines, growth factors, and apoptotic bodies from hepatocytes[18]. Chronic liver injury involves HSCs undergoing phenotypic activation towards myofibroblasts, which is characterized by increased expression of cell markers such as alpha-smooth muscle actin (α -SMA) and collagen. In addition, transforming growth factor-beta 1 (TGF- β 1) inhibits liver regeneration during HSC to myofibroblast differentiation, ultimately leading to hepatic fibrosis[19].

OS-MEDIATED HEPATIC FIBROSIS

OS refers to the imbalance between the normal oxidant scavenging enzyme system [such as superoxide dismutase (SOD), catalase, and glutathione (GSH)] and the production of ROS in the cells, which is considered a key driving factor in hepatic fibrosis[20]. Oxidants, also known as ROS, include superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen[21]. In addition, they also contain some nitrogen oxides, lipid peroxide radicals, and

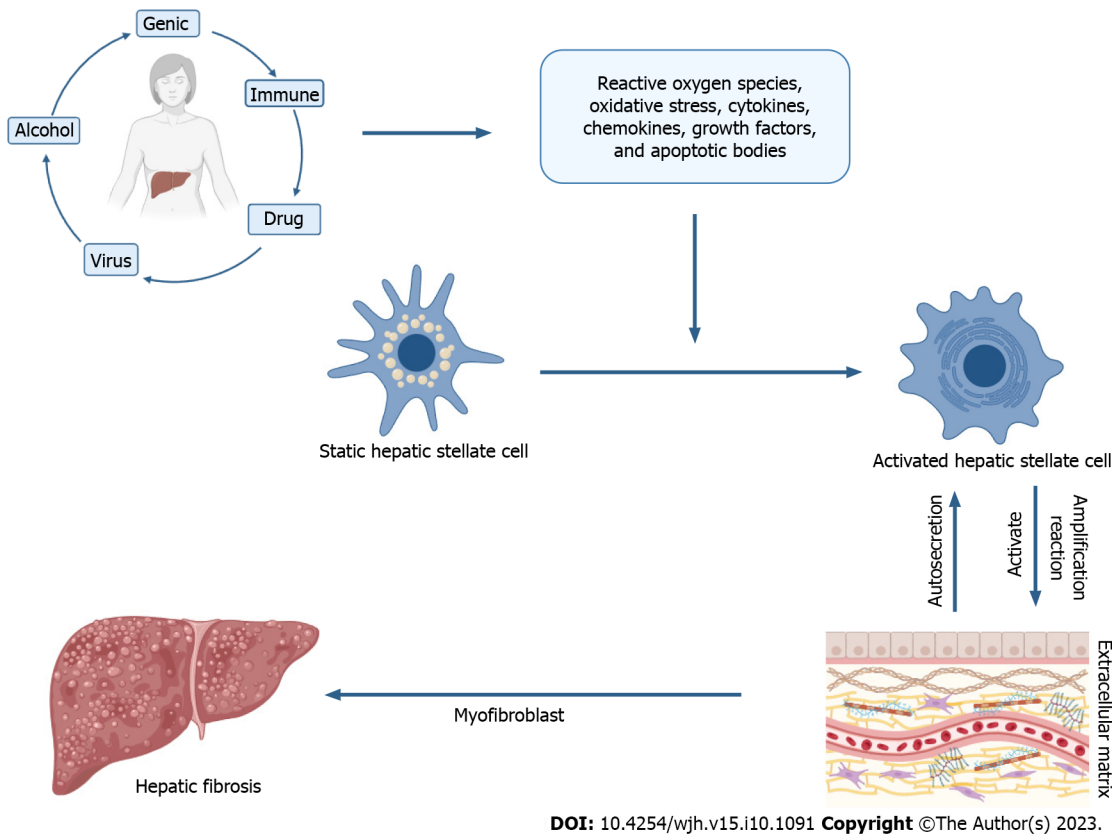


Figure 1 The mechanism of hepatic fibrosis. Due to various factors such as alcohol abuse, viral hepatitis infection, genetic abnormalities, alcoholic fatty liver disease, autoimmune diseases, and medications, the body may produce an excessive amount of reactive oxygen species, leading to oxidative stress. At the same time, these factors may also induce cells to release cytokines, chemokines, growth factors, and apoptotic bodies, as well as activate hepatic stellate cells (HSC) and transform them into myfibroblasts. Consequently, large amounts of extracellular matrix (ECM) substances, such as collagen, non-fibrillar collagens, glycosaminoglycans, and proteoglycans, are autosecreted. The presence of these ECM substances can further stimulate the autosecretion of HSCs, ultimately resulting in fibrosis and impaired liver function.

hypochlorous acid. The process of oxidant formation begins with oxygen being reduced to water, resulting in the production of free radicals such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals[22].

Under physiological conditions, ROS are the result of normal cellular metabolism and are maintained in dynamic equilibrium with antioxidants[23]. Under pathological conditions, excess ROS can stimulate pathological oxidative-reductive signal transduction, leading to OS. Various organic compounds such as DNA, lipids, carbohydrates, and proteins are structurally damaged, resulting in cell damage and various diseases[24]. Lee *et al*[25] first demonstrated a possible molecular link between enhanced lipid peroxidation and induced collagen gene expression in cultured fibroblasts, suggesting that OS plays a direct pathogenic role in hepatic fibrogenesis. Sustained OS in the liver directly or indirectly affects hepatocytes and alters the structure of cell membranes and organelles, causing damage, necrosis, and apoptosis[26]. These processes lead to cell damage and the release of various cytokines and growth factors, inducing quiescent HSC activation into myfibroblasts expressing α -SMA as a characteristic marker[27]. Activated HSCs lose lipid droplets (vitamin A), rapidly proliferate, and upregulate many genes, especially collagen, fibronectin, laminin, and hyaluronic acid, beginning to increase the synthesis of connective tissue proteins, especially collagen, leading to fibrosis formation and further development into liver cirrhosis and even liver cancer[19,28]. In addition, excess ROS also enhance the secretion of the fibrogenic factor TGF- β 1, which is highly involved in HSC activation, exacerbating ECM deposition in the liver and progressing to hepatic fibrosis[29]. The mechanism of OS-mediated hepatic fibrosis is shown in Figure 2.

UNDERSTANDING HEPATIC FIBROSIS FROM TCM PERSPECTIVE

Ancient literature did not have a clear concept of “hepatic fibrosis” as a disease name. Based on its main clinical manifestations of hypochondriac pain, palpable masses in the hypochondrium, and jaundice, modern physicians categorize it under disease categories such as distension and swelling, hypochondriac pain, accumulation, and jaundice[6]. The Ling Shu section of the Huangdi Neijing states: “If the evil is in the liver, then there is pain in both flank regions, the patient feels cold, and stagnant blood circulates within, causing restricted joint movements, and occasional foot swelling. Acupuncture at Jia Jian was used to activate the meridian around the liver area and warm up the stomach, extract blood through veins to eliminate stagnant blood, and take out the green vein by the ear to alleviate cramps[30].” The Huangdi Neijing says: “Wind, cold, and dampness combined cause obstruction of channels and collaterals, known as arthralgia.

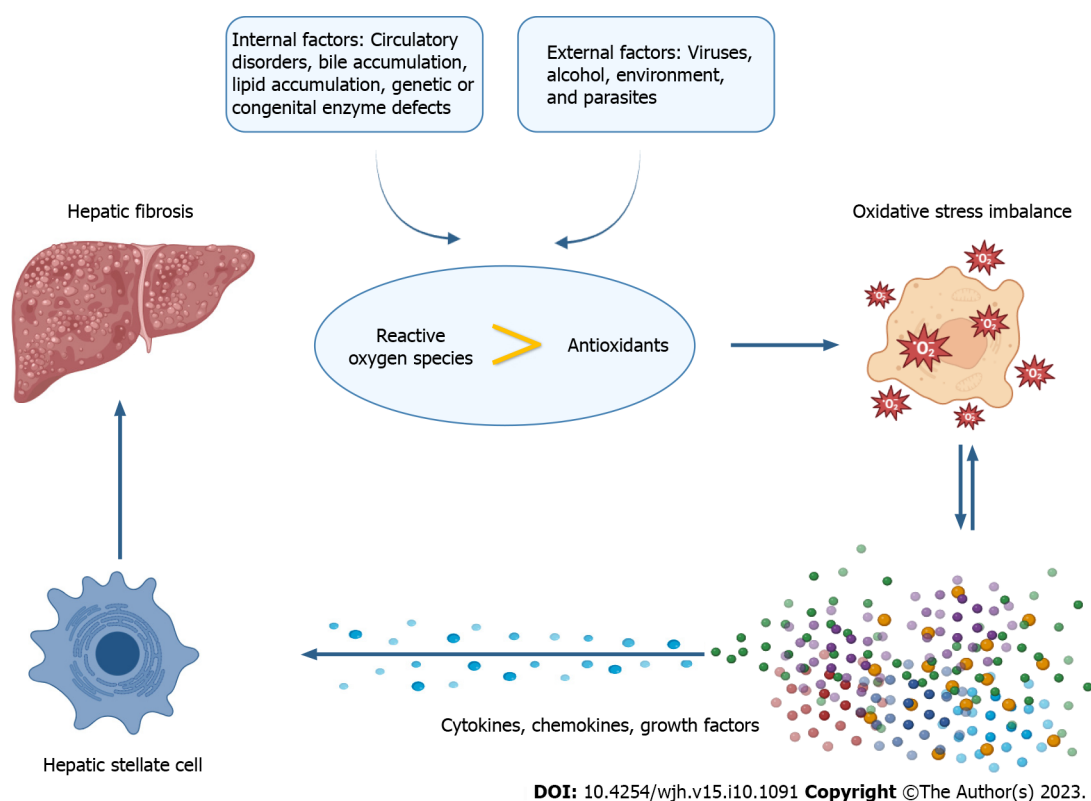


Figure 2 The mechanism of oxidative stress-mediated hepatic fibrosis. Circulatory disorders, bile accumulation, lipid accumulation, genetic or congenital enzyme defects, as well as factors such as viruses, alcohol, environment, and parasites, can all contribute to an imbalance between the production of reactive oxygen species and the body's ability to remove them, resulting in oxidative stress. This imbalance can further stimulate the secretion of cytokines, chemokines, and growth factors, which in turn activate hepatic stellate cells and contribute to the development of hepatic fibrosis.

Furthermore, if this occurs in spring, it is called tendon arthralgia. Tendon arthralgia continues stubbornly and is further affected by evil forces, which reside in the liver interior. All organs have junctions, so if an illness remains lingering, it will settle in the junction of that organ. Since the liver's junction is with the tendons, the arthralgia continues, and when affected by evil forces, it settles in the liver[31]. Therefore, the TCM understanding of the pathogenesis of hepatic fibrosis can be summarized as weakened vital qi, allowing external pathogenic factors such as excessive exposure to the "Six Pathogens" or inappropriate emotional responses from the "Seven Emotions" to invade, resulting in Qi stagnation and blood stasis[32]. This progression is often slow and persistent, ultimately leading to hepatic fibrosis. Based on classic single herbal extracts and TCM formulas, many effective preventive and therapeutic TCM formulas have been developed and applied clinically. Currently, TCM monomers, single herbal extracts, and TCM formulas can regulate HSCs and ECM expression levels by affecting OS, achieving a state of balance between yin and yang in the body, and thereby preventing and treating hepatic fibrosis[33]. Therefore, this article analyzes and discusses the research progress in preventing and treating hepatic fibrosis through the inhibition of OS by using TCM monomers, single herbal extracts, and TCM formulas, based on recent domestic and international studies on hepatic fibrosis, in order to provide a theoretical basis for future research.

MECHANISMS OF TCM IN ANTI-FIBROSIS

As TCM has shown good therapeutic effects in various chronic diseases, its role and mechanism in preventing and treating hepatic fibrosis have attracted widespread attention from scientists. Scholars from various countries have begun using modern pharmacological research methods to explore the mechanisms of TCM in anti-fibrosis. It has been confirmed that TCM monomers (such as flavonoids, glycosides, alkaloids, and polysaccharides), single herbal extracts (such as *Salvia miltiorrhiza*, *Ginkgo biloba* leaf, clove basil, *Ceratonia siliqua* pod extract, grape seed, pomegranate extract, *Taraxacum officinale* root extract, and *Myrtus communis*), and TCM formulas [such as Yin-Chen-Hao-Tang (YCHT), Xiaochaihu Tang (XCHT), Fu Zheng Hua Yu Fang, Chunggan extract, and Huangjia Ruangan Granule] can be used to inhibit OS and prevent and treat hepatic fibrosis (Figure 3).

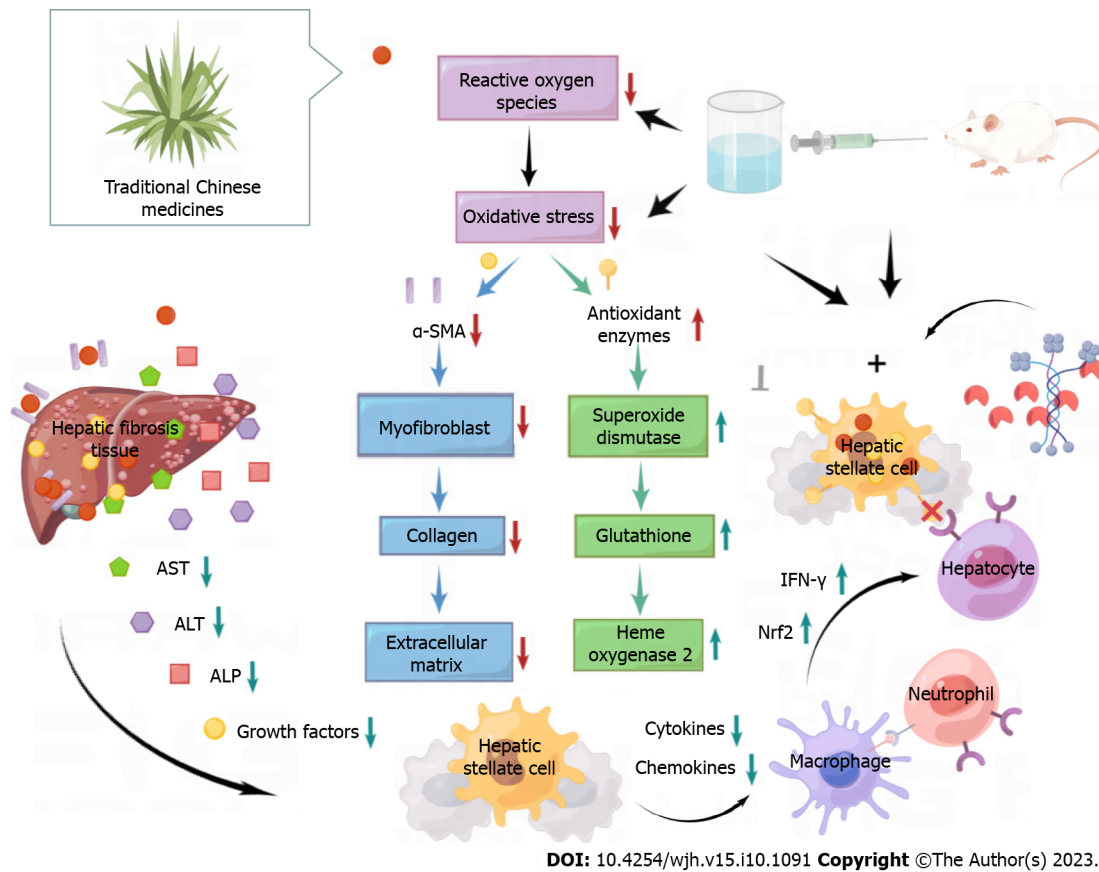


Figure 3 Treatment of hepatic fibrosis by oxidative stress mediated by traditional Chinese medicine. Traditional Chinese medicine employs various mechanisms to reduce the production of reactive oxygen species in the body, thereby suppressing oxidative stress reactions. They can enhance the secretion of antioxidant enzymes such as superoxide dismutase, glutathione, and heme oxygenase 2, as well as increase the activity of interferon- γ and nuclear factor erythroid 2-related factor. Moreover, traditional Chinese medicine can inhibit the secretion of growth factors, cytokines, chemokines, macrophages, and neutrophils. They can also hinder the activation of quiescent hepatic stellate cells into myofibroblasts and facilitate the degradation of extracellular matrix components like collagen. These actions contribute to the protection of liver function and hepatocytes, ultimately mitigating and reversing hepatic fibrosis. ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; α -SMA: Alpha-smooth-muscle actin; IFN- γ : Interferon- γ ; Nrf2: Nuclear factor erythroid 2-related factor.

TCM MONOMERS

In recent years, numerous experimental studies have demonstrated that TCM monomers, such as flavonoids, glycosides, alkaloids, and polysaccharides, can reduce the activation rate of HSCs by inhibiting OS and reducing excessive ECM deposition. This in turn can suppress hepatic fibrosis and connective tissue proliferation or improve liver function and delay the progression of hepatic fibrosis.

FLAVONOIDS

Flavonoids are a class of compounds that belong to the family of polyphenols. They are widely found in plant-based foods such as vegetables, fruits, and grains[34]. Flavonoids are known for their beneficial effects on human health, such as antioxidant and anti-inflammatory properties[35]. The most common flavonoids include quercetin, kaempferol, and myricetin, which are found in many fruits and vegetables[34]. Flavonoids have been linked to a reduced risk of chronic diseases such as cardiovascular disease, cancer, and diabetes[36]. Briefly, the consumption of flavonoid-rich foods is an important part of a healthy diet. Extensive pharmacological research has shown that flavonoids possess the ability to inhibit the pathological production of ROS, suppress OS, boost the antioxidant capacity of the body, and offer protection against hepatic fibrosis[37].

Quercetin is an important plant chemical substance belonging to the polyphenolic flavonoid group[38]. The chemical formula of quercetin is $C_{15}H_{10}O_7$, and its structure shares a common flavonoid nucleus composed of two benzene rings linked by a heterocyclic pyran ring[39]. Quercetin is commonly found in various fruits and vegetables, including apples, berries, cherries, red leaf lettuce, onions, and asparagus, with small amounts present in pepper, broccoli, peas, and tomatoes[40]. It is well known that onions contain the highest levels of quercetin[41]. Quercetin is one of the most extensively researched flavonoids and has been found to exhibit exceptional antioxidant activity. Its effects on GSH and ROS activity, as well as its regulation of various signaling pathways including heme oxygenase 1/nuclear factor erythroid 2-related factor (Nrf2), mitogen-activated protein kinase (MAPK), Toll-like receptor 4 (TLR4)/phosphatidylin-

ositol-3-kinase (PI3K), and 5'adenosine monophosphate-activated protein kinase have been demonstrated in numerous studies[42]. Studies have also shown that quercetin can enhance the activities of antioxidant enzymes like SOD and increase GSH levels. Furthermore, it can inhibit OS, down-regulate inflammatory cytokine expression, and reduce tissue histopathological changes induced by thioacetamide, thus mitigating hepatic fibrosis[43]. In addition, Khodarahmi *et al* [44] proposed that quercetin can improve hepatic fibrosis by inhibiting ROS-related OS-mediated inflammatory cascades. Concisely, these findings suggest that quercetin has potential therapeutic benefits for hepatic fibrosis through its ability to enhance antioxidant enzyme activities, reduce OS and inflammation, and inhibit ROS-mediated cascades. However, more research is needed to fully understand the mechanism of action and optimal dosage of quercetin for treating hepatic fibrosis.

Isorhamnetin, with the chemical formula $C_{16}H_{12}O_7$, is a 3'-O-methylated gut metabolite of quercetin[45]. Isorhamnetin belongs to the flavonoid family, more specifically the flavonol group[46]. It can be found in several plants, such as sorbus, ginkgo leaves, or cactus, which have traditionally been used as medicinal plants in various cultures[47]. *In vitro*, isorhamnetin can scavenge diphenylpicrylhydrazyl and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) radicals, inhibit liver mitochondrial lipid peroxidation, and exhibit antioxidant activity[48]. Furthermore, isorhamnetin can block TGF- β 1-induced ROS production and GSH depletion, reduce phosphorylated Smad3, TGF- β 1, α -SMA, and plasminogen activator inhibitor-1 expression, and collagen expression in primary mouse HSCs and LX-2 cells, alleviate OS, and inhibit HSC activation, thereby preventing hepatic fibrosis[49]. These findings suggest that isorhamnetin may have potential therapeutic applications for hepatic fibrosis.

Naringin is a natural organic compound with the molecular formula $C_{15}H_{12}O_5$ [50]. Naringin and its glycosides are present in various herbs and fruits, including grapefruit, Buddha's hand citron, lime, tart cherry, tomato, cocoa, Greek hay, water mint, and legumes[51]. Due to its hydroxyl substituents, naringin exhibits high reactivity towards ROS and reactive nitrogen species and has strong inhibitory effects on lipid peroxidation in mouse liver, brain, and heart tissues [52]. In 2017, Hernández-Aquino *et al*[53] reported that administration of naringin could potentially prevent an increase in liver enzymes such as alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase, and GSH peroxidase (GSH-Px). Additionally, naringin was shown to enhance the body's antioxidant capacity and effectively prevent liver inflammation, hepatocyte necrosis, and hepatic fibrosis induced by carbon tetrachloride (CCl_4)[53]. Building on this work, Hernández-Aquino *et al*[54] conducted further research in 2019 and found that naringin has the potential to inhibit OS and exert its anti-fibrotic effect by blocking the nuclear transcription factor- κ B (NF- κ B), TGF- β -Smad3, and c-Jun N-terminal kinase-Smad3 pathways. These findings suggest that naringin could be a promising candidate for treating human fibrosis.

Additionally, *Mallotus apelta* (Lour.) Muell.Arg. leaf and *Bidens bipinnata* L. contain total flavonoids along with other beneficial compounds such as puerarin, hesperidin, alpinetin, fisetin, glabridin, morin, and astilbin. These compounds have been shown to inhibit OS and promote a stable internal environment within the body, thereby improving hepatic fibrosis (Table 1).

GLYCOSIDES

Glycosides are a diverse group of biologically active compounds that are widely distributed in the plant kingdom[55]. They consist of a sugar molecule linked to a non-sugar compound, such as a flavonoid or terpenoid. Glycosides have been extensively studied for their pharmacological properties, which include anti-inflammatory, antibacterial, antifungal, and antioxidant effects[56]. In particular, glycosides have been found to possess potent antioxidant properties that can prevent or reduce OS in various tissues and organs, including the liver[57].

Saikosaponin-D is a type of glycoside monomer component extracted from the dried roots of *Bupleurum chinense* DC. and *Bupleurum scorzonrifolium* Willd, both plants belonging to the Umbelliferae family[58]. Its molecular formula is $C_{42}H_{68}O_{13}$ [58]. Saikosaponin-D possesses various pharmacological effects such as antioxidant, sedative, antiviral, anti-inflammatory, immune-regulatory, hepatoprotective, and anticancer activities[59]. Saikosaponin-D can delay the development of hepatic fibrosis by alleviating liver cell damage caused by OS[57]. Researchers such as Que *et al*[60] have proposed that saikosaponin-D may downregulate the ROS/MAPK signaling pathway. This not only significantly inhibits the proliferation and activation of HSC-T6 cells induced by OS but also reduces the deposition of the ECM, such as tissue inhibitors of TGF- β 1, hydroxyproline, collagen-1, and matrix metalloproteinase (MMP)-1, which indicates its potential as a therapeutic agent for hepatic fibrosis[60]. However, despite its promising pharmacological properties, the clinical use of saikosaponin-D is limited due to its low bioavailability and poor water solubility. Further research is needed to develop effective delivery systems and optimize its pharmacokinetic properties to allow for its use in clinical settings.

Resveratrol glucoside is a polyphenol and monocrystalline natural compound belonging to the stilbene class[61]. Vitaceae, Liliaceae, and Leguminosae families are the important sources of resveratrol glucoside extraction[62]. It is mainly isolated from the rhizome and roots of *Polygonum cuspidatum*, and also found in daily foods such as grapes and red wine[62]. Various studies have shown that resveratrol glucoside has a variety of pharmacological activities, such as anti-inflammatory, anti-apoptotic, anti-tumor, lipid-lowering, and cardiovascular protective effects, particularly strong antioxidant pharmacological activity[63]. Resveratrol glucoside has been shown to have antioxidant biological activity and therapeutic action on many liver diseases, including hepatic fibrosis. For example, resveratrol glucoside has been found to inhibit the production of 4-hydroxydecanoic acid in the liver and the expression of nicotinamide adenine dinucleotide phosphate oxidase 4, thereby reducing OS and inflammation and improving chronic liver injury and fibrosis [64,65]. Moreover, research has demonstrated that resveratrol glucoside can also downregulate the nicotinamide adenine dinucleotide phosphate oxidase 4 enzyme, thus decreasing TLR4/NF- κ B p65 signaling pathway-related inflammatory

Table 1 Flavonoids improve hepatic fibrosis by inhibiting oxidative stress

No.	Flavonoids	Model	Upregulated molecules	Downregulated molecules	Mechanism	Ref.
1	<i>Mallotus apelta</i> (Lour.) Muell.Arg. leaf	Rat	IkBa, SOD, GSH-Px	HYP, PC-III, Col-I, HA, LN, α -SMA, Col-III, MDA, TNF- α , IL-1 β , IL-6, MMP-2/9, TIMP-1, TGF- β 1/Smad, IKK β , NF- κ B p65, pNF- κ Bp65, IkBa, p-IkBa	Improving hepatic fibrosis and reducing ECM accumulation are related to inhibiting OS and regulating the TGF- β 1/Smad signaling pathway and NF- κ B-dependent inflammatory response	Zhang <i>et al</i> [117]
2	<i>Bidens bipinnata</i> L.	Rat	SOD, GSH-Px	NF- κ B, α -SMA, TGF- β 1	Inhibiting OS to improve liver injury and protect rats from CCl ₄ -induced hepatic fibrosis	Yuan <i>et al</i> [118]
3	Puerarin	Rat	SOD, CAT	TG, TCHO, LDL, α -SMA, Col-I/III, MDA, IL-1 β , IL-6, TNF- α , MCP-1, NF- κ B/p65, TGF- β , TGF- β /Smad2/3	Inhibiting OS and inflammation associated with NF- κ B signal inactivation, thereby blocking the upregulation of pro-inflammatory cytokines (IL-1 β and TNF- α) and chemokines (MCP-1), ultimately improving hepatic fibrosis	Hou <i>et al</i> [119]
4	Hesperidin	Mice		ROS	Regulating liver OS and alleviating mitochondrial dysfunction to reduce fibrosis	Li <i>et al</i> [120]
5	Alpinetin	Mice	IL-10, CAT, GSH-Px, SOD, GSH, Nrf2	HYP, α -SMA, fibronectin, α 1(I) procollagen, IL-1 β , IL-6, TNF- α , Cox-2, iNOS, MDA, VEGF, VEGFR2, PDGF- β R, HIF-1 α	Preventing and treating hepatic fibrosis by inhibiting the anti-inflammatory activity mediated by NLRP3 and the anti-OS activity mediated by Nrf2	Zhu <i>et al</i> [121]
6	Fisetin	Rat	GSH, GSK-3 β	MDA, TNF- α , IL-6, TGF- β 1, Col-I, TIMP-1, Wnt3a, β -catenin, α -SMA, Cyclin D1	Inhibiting liver OS can suppress Wnt/ β -catenin pathway and inhibit HSC activation and proliferation, regulate MMP-9 and TIMP-1, and suppress multiple pro-fibrotic factors, to prevent and treat hepatic fibrosis	El-Fadaly <i>et al</i> [122]
7	Glabridin	Mice	PPAR- γ , GSH, T-AOC	α -SMA, fibronectin, Col- α 1(I), MDA	Activation of PPAR γ can inhibit inflammation and OS, thereby inhibiting HSC activation and hepatic fibrosis	Zhang <i>et al</i> [123]
8	Morin	Rat	GSH	NO, HYP, TNF- α , iNOS, NF- κ B (p65)	Receiving MDA and nitric oxide levels elevation, and restoring GSH to normal levels can inhibit OS and improve hepatic fibrosis	Heeba and Mahmoud [124]
9	Astilbin	Rat	SOD, GSH, GCLC, GCLM, HO-1, NQO1, Nrf2	TGF- β , Col-I/III, HYP, TNF- α , IL-1 β , IL-6, MDA	Significant reduction in collagen production, inflammation and OS <i>in vivo</i> can prevent CCl ₄ -induced hepatic fibrosis in rats	Sun <i>et al</i> [125]

α -SMA: Alpha-smooth-muscle actin; ECM: Extracellular matrix; OS: Oxidative stress; TGF- β 1: Transforming growth factor-beta 1; NF- κ B: Nuclear transcription factor- κ B; SOD: Superoxide dismutase; GSH: Glutathione; GSH-Px: Glutathione peroxidase; IL: Interleukin; TNF: Tumor necrosis factor; ROS: Reactive oxygen species; Nrf2: Nuclear factor erythroid 2-related factor; HSC: Hepatic stellate cell.

reactions and macrophage expression, which suggests that it could be an effective therapeutic agent for preventing and treating hepatic fibrosis[66]. To sum up, resveratrol glucoside shows promise as a natural compound for preventing and treating chronic liver injury and fibrosis. Further research is needed to fully understand its mechanisms of action and optimal dosage for therapeutic use.

Geniposide is an organic compound with the molecular formula C₁₇H₂₄O₁₀[67]. It is derived from the dried mature fruit of *Gardenia jasminoides* Ellis, a plant belonging to the Rubiaceae family[68]. Geniposide is mainly found in *Gardenia jasminoides*, but has also been detected in other commonly used Chinese herbal medicines such as *Eucommia ulmoides*, *Rehmannia glutinosa*, and *Scutellaria baicalensis*[68]. Geniposide not only upregulates endogenous antioxidant enzymes to slow down cell damage, but also increases the activity of antioxidant enzymes and pathways such as liver lipid peroxidation, GSH S-transferases, GSH, GSH-Px, and copper- and zinc-containing SOD, which can prevent OS damage, protect hepatocytes, and improve hepatic fibrosis[69]. The study by Yang *et al*[70] investigated the protective effects of geniposide on hepatic fibrosis in a rat model induced by CCl₄ administration. The researchers found that geniposide treatment significantly reduced hepatic fibrosis and improved liver function, as evidenced by decreased levels of serum ALT, aspartate aminotransferase (AST), and ALP. Further analysis revealed that geniposide exerted its anti-fibrotic effects through multiple mechanisms[70]. First, geniposide increased the activities of two important antioxidant enzymes, SOD and GSH-Px, which scavenge free radicals and protect cells from oxidative damage. This was accompanied by a reduction in the levels of malondialdehyde (MDA), a biomarker of lipid peroxidation, in the liver tissue[70]. In brief, the study suggested that geniposide has potential as a therapeutic agent for hepatic fibrosis by targeting OS. However, further studies are needed to confirm these findings in human subjects and to explore the optimal dosage and duration of geniposide treatment.

In addition, glycoside compounds such as baicalin, vitexin, and forsythoside A (Table 2) can also improve hepatic fibrosis by inhibiting the body's OS, regulating intestinal flora bile acid metabolism, increasing antioxidant and phase II

Table 2 Glycosides improve hepatic fibrosis by inhibiting oxidative stress

No.	Glycosides	Model	Upregulated molecules	Downregulated molecules	Mechanism	Ref.
1	Wogonoside	Rat	SOD, GSH, IL-10	HA, LN, HYP, MDA, TNF- α , IL-1 β , IL-6, TGF- β , MMP-2/9, Smad-3, PI3K/Akt/mTOR, NF- κ B p65, PI3K/Akt/mTOR/p70S6K, α -SMA, Col-I	Inhibition of OS can improve hepatic fibrosis	Wang <i>et al</i> [126]
2	Hyperoside	Mice	SOD, GSH-Px, CAT, GSH, Nrf2	GOT, GPT, MDA, TGF- β , Col-I/III	Activating Nrf2 nuclear translocation, inhibiting OS to increase antioxidant and phase II detoxifying enzyme activity can improve hepatic fibrosis	Zou <i>et al</i> [127]
3	Forsythiaside A	Mice	SOD, GSH, CAT, GSH-Px, p450 7a1, FXR, SHP, LRH-1, BSEP, NTCP, OATP-1	HA, LN, PC-III, Col-I/IV, HYP, α -SMA, TNF- α , IL-1 β , IL-6, LCA, DCA, HDCA, β -MCA, alloLCA, NorDCA, NorCA, CA, FGF-R4, MRP-2	Inhibiting OS and inflammation, regulating gut microbiota and BA metabolism can improve hepatic fibrosis	Fu <i>et al</i> [128]

α -SMA: Alpha-smooth-muscle actin; OS: Oxidative stress; SOD: Superoxide dismutase; GSH: Glutathione; GSH-Px: Glutathione peroxidase; IL: Interleukin; Nrf2: Nuclear factor erythroid 2-related factor.

detoxification enzyme activity. To recap, the evidence suggests that glycosides can prevent or reduce hepatic fibrosis by inhibiting ROS production, reducing OS, and modulating HSC activation. These findings highlight the potential of glycosides as therapeutic agents for hepatic fibrosis and other OS-related diseases. However, further studies are needed to elucidate the molecular mechanisms underlying the protective effects of glycosides and identify optimal doses and treatment regimens.

ALKALOIDS

Alkaloids are a class of naturally occurring organic compounds that are characterized by their bitter taste and basic properties[71]. They are found in many plants and have a wide range of biological activities, including analgesic, anti-inflammatory, and anti-cancer properties. Alkaloids have complex interactions with ROS and hepatic fibrosis[72].

Some alkaloids have protective effects against hepatic fibrosis by reducing ROS production and promoting antioxidant activity. Further research is needed to better understand the mechanisms underlying these effects and to identify new alkaloids with potential therapeutic applications in hepatic fibrosis.

Berberine is a naturally occurring compound found in various plants such as goldenseal, barberry, and oregon grape [73]. It has been widely used in traditional medicine for its anti-inflammatory, anti-microbial, and anti-diabetic properties [74]. In recent years, there has been growing interest in the potential of berberine as a treatment for hepatic fibrosis. Studies have shown that berberine has potent antioxidant properties that help reduce OS and ROS levels in the liver[75]. It achieves this by activating various cellular defense mechanisms that protect liver cells from oxidative damage[75]. Furthermore, studies suggest that berberine can prevent the activation of HSCs, which are responsible for producing the scar tissue that leads to hepatic fibrosis[76]. Domitrović *et al*[77] demonstrated that the administration of high-dose berberine (9 mg/kg) is effective in reducing OS, decreasing the expression of tumor necrosis factor- α (TNF- α) and TGF- β 1, increasing MMP-2 levels, and promoting the removal of fibrous deposits to ameliorate hepatic fibrosis. In essence, these findings suggest that berberine has great potential as a therapeutic agent in the treatment of hepatic fibrosis. By reducing OS and preventing the activation of HSCs, berberine may help slow or even reverse the progression of hepatic fibrosis. However, further research is necessary to fully understand the mechanisms through which berberine exerts its beneficial effects on hepatic fibrosis.

Betaine, also known as trimethylglycine, is a naturally occurring compound found in many foods, including spinach, beets, and whole grains[78]. It is used as a dietary supplement to improve athletic performance, promote liver health, and reduce the risk of liver disease[79]. Research suggests that betaine may help to alleviate hepatic fibrosis by reducing OS. In a study conducted by Bingül *et al*[80], betaine supplementation was found to significantly reduce ROS levels, decrease lipid peroxidation, and increase antioxidant enzyme activity in rats with hepatic fibrosis induced by CCl₄ exposure. Additionally, betaine treatment reduced collagen deposition and improved liver function in these rats, indicating that it may have therapeutic potential for hepatic fibrosis[81]. Another study conducted by Kim *et al*[82] investigated the effects of betaine on OS and fibrosis in liver cells. The researchers found that betaine treatment reduced ROS levels and lipid peroxidation, increased GSH levels (an important antioxidant in the body), and inhibited the expression of fibrotic markers in HSCs, the primary cells responsible for hepatic fibrosis. These results suggest that betaine may exert its anti-fibrotic effects by modulating OS and reducing fibrogenic signaling pathways in liver cells[82]. In conclusion, the relationship between betaine and hepatic fibrosis is complex, but emerging evidence suggests that betaine may help to alleviate hepatic fibrosis by reducing OS, inhibiting fibrogenic signaling pathways, and promoting liver function. Further research is needed to fully elucidate the mechanisms underlying betaine's therapeutic effects on hepatic fibrosis and determine optimal dosages and treatment durations for clinical use.

Lycorine is a natural alkaloid that is found in various plant species such as the Amaryllidaceae family[83]. It has been known to possess multiple pharmacological properties, including anti-cancer, anti-inflammatory, and antiviral activities [84]. Recently, lycorine has also been studied for its effect on hepatic fibrosis, a chronic condition that occurs due to the accumulation of ECM proteins in the liver tissue. Lycorine has been shown to inhibit ROS production and reduce OS, thereby reducing HSC activation and regulating the fibrotic process[83]. Furthermore, lycorine may also have a protective effect against liver injury caused by OS. In a study conducted on animal models of acute liver injury induced by CCl₄, lycorine was found to prevent liver damage by reducing OS and inflammation in liver tissue[85]. To conclude, the relationship between lycorine, ROS, OS, and hepatic fibrosis is complex and multifaceted. More research is needed to explore the potential therapeutic effects of lycorine in hepatic fibrosis and other related liver diseases. However, the current evidence suggests that lycorine may hold promise as a natural therapeutic agent for hepatic fibrosis.

To put it briefly, alkaloids have shown potential as therapeutic agents for the treatment of hepatic fibrosis. However, more research is needed to determine their efficacy and safety, especially at higher doses. It is important to work with a healthcare professional to determine the best course of action for managing hepatic fibrosis and to monitor liver function regularly.

POLYSACCHARIDES

Polysaccharides are complex carbohydrates that play an important role in the body's physiological processes[86]. They are found in a variety of sources, including plants, fungi, and animals, and are known for their ability to confer a range of health benefits[86]. One area where polysaccharides have shown particular promise is in the treatment of hepatic fibrosis. Recent research has suggested that polysaccharides may offer a promising alternative for managing hepatic fibrosis. In particular, studies have shown that certain polysaccharides have antioxidant properties, which can help reduce OS in the liver. OS is known to play a key role in the development and progression of hepatic fibrosis.

Cordyceps is a type of fungus that has been used for centuries in traditional medicine to treat a variety of ailments[87]. In recent years, researchers have been investigating the therapeutic potential of *Cordyceps* polysaccharides, one of the main bioactive compounds found in the fungus[88]. *Cordyceps* polysaccharides have been shown to have antioxidant and anti-inflammatory properties, making them a promising candidate for treating hepatic fibrosis, a condition characterized by scarring and damage to the liver[89]. *Cordyceps* polysaccharides protect hepatocytes from hydrogen peroxide-induced mitochondrial dysfunction by reducing ROS production and regulating mitochondrial apoptotic signaling *via* cytochrome C, apoptosis regulator Bax, and mitochondrial-related apoptotic proteins in HepG2 cells[90]. In addition, studies have shown that *Cordyceps* polysaccharides can reduce the release of pro-inflammatory cytokines and cell apoptosis by regulating TLR4/myeloid differentiation factor 88/NF- κ B, Bcl-2/Bax, and caspase family signaling pathways, thereby reducing OS, serum enzymes, α -SMA, Col-III, TGF- β 1, p-Smad3, and collagen volume fraction, inhibiting OS, enhancing the body's antioxidant defense system, and improving hepatic fibrosis[91]. Recapitulating, *Cordyceps* polysaccharides have demonstrated hepatoprotective effects against liver injury caused by OS. They can regulate various signaling pathways to promote liver cell survival, reduce fibrosis, and improve liver function. These findings suggest that polysaccharides may be a promising therapeutic agent for liver diseases.

The relationship between polysaccharides, OS, and hepatic fibrosis is complex, and additional research is needed to fully understand the mechanisms underlying this relationship. However, these findings suggest that polysaccharides may offer a promising new avenue for the treatment of hepatic fibrosis.

SINGLE HERBAL EXTRACTS

Single herbal extracts such as *Salvia miltiorrhiza*, *Ginkgo biloba* leaf, clove basil, *Ceratonia siliqua* pod extract, grape seed, pomegranate extract, *Taraxacum officinale* root, and *Myrtus communis* have demonstrated significant potential in combating hepatic fibrosis. These extracts target OS pathways, regulate HSC activation and apoptosis, and inhibit collagen deposition in liver tissue, as outlined in Table 3.

Salvia miltiorrhiza, also known as Danshen, is a TCM that has been used for centuries to treat various ailments, including liver disease[92]. Recent studies have shown that one of the mechanisms by which *Salvia miltiorrhiza* exerts its hepatoprotective effects is through the modulation of OS pathways in the liver[93]. Research has demonstrated that *Salvia miltiorrhiza* can alleviate hepatic fibrosis by reducing the generation of ROS and the consequent activation of HSCs[94]. In a recent study, Zhang *et al*[94] investigated the effect of *Salvia miltiorrhiza* on ROS-induced hepatic fibrosis in rats. The researchers found that treatment with *Salvia miltiorrhiza* significantly reduced the levels of ROS and lipid peroxidation products in the liver tissue, and also inhibited the activation of HSCs[94]. Furthermore, they observed that *Salvia miltiorrhiza* treatment increased the expression of antioxidant enzymes, such as SOD and catalase, which help protect against OS in the liver[95]. Another study by Wang *et al*[96] explored the potential molecular mechanisms underlying the anti-fibrotic effects of *Salvia miltiorrhiza*. The researchers found that *Salvia miltiorrhiza* could inhibit the expression of fibrogenic genes in HSCs, such as Col-I and α -SMA, by downregulating the activity of the TGF- β signaling pathway, which is known to be a key regulator of fibrogenesis in the liver[96]. Moreover, they observed that *Salvia miltiorrhiza* treatment reduced the production of ROS and enhanced the activity of antioxidant enzymes in HSCs, which may contribute to its anti-fibrotic effects[97]. Summarily, these studies provide evidence that *Salvia miltiorrhiza* can protect against hepatic fibrosis by modulating OS pathways in the liver. Further research is needed to fully understand the molecular mechanisms underlying this effect and to explore the potential of *Salvia miltiorrhiza* as a therapeutic agent for

Table 3 Single herbal extracts improve hepatic fibrosis by inhibiting oxidative stress

No.	Single herbal extracts	Model	Upregulated molecules	Downregulated molecules	Mechanism	Ref.
1	<i>Salvia miltiorrhiza</i>	Mice	SOD, GSH	Col-1/III, TGF- β , MDA, IL-1 α , TNF- α	Reducing MDA content, increasing SOD activity and GSH content, and suppressing OS while also reducing TNF- α and IL-1 α can improve hepatic fibrosis	Zhang <i>et al</i> [94]
2	<i>Ginkgo biloba</i> leaf	Rat		MDA, TGF- β 1, Col-1	Effectively regulating the OS thioacetamide-induced hepatic fibrosis	Al-Attar <i>et al</i> [100]
3	Clove basil	Rat	CAT	α -SMA, Col- α	Inhibiting OS can significantly suppress HSC activation, as well as the expressions of α -SMA and Col- α , exhibiting its anti-hepatic fibrosis properties	Chiu <i>et al</i> [103]
4	<i>Ceratonia siliqua</i> pod	Mice	GSH, SOD, CAT, GST, GPx, GR	TIMP-2, NO	Inhibiting the production of LPO and NO, increasing the content of GSH, and restoring the activity of antioxidant enzymes can suppress OS, granuloma formation, and hepatic fibrosis	Al-Olayan <i>et al</i> [129]
5	Grape seed	Rat	AOC, GSH	TNF- α , MDA, MPO	Inhibiting neutrophil infiltration and lipid peroxidation, suppressing OS, restoring the oxidative and antioxidant status in tissues can help protect against hepatic fibrosis	Dulundu <i>et al</i> [130]
6	Pomegranate	Rat	SOD, GST, CAT, Nrf2	NF- κ B, α -SMA, Cox-2	Reducing OS by regulating Nrf2 and NF- κ B can eliminate hepatic fibrosis	Husain <i>et al</i> [131]
7	<i>Taraxacum officinale</i> root	Mice	SOD, mt I/II	α -SMA	Inhibiting OS, inducing HSC inactivation and enhancing liver regeneration capacity are effective in the treatment of hepatic fibrosis	Domitrović <i>et al</i> [132]
8	<i>Myrtus communis</i>	Rat	GSH, SOD	TNF- α , IL-1 β , MDA, MPO, TGF- β	Its antioxidant and free radical scavenging activities protect liver tissue from OS damage after bile duct ligation, thereby exerting its anti-fibrotic effects	Sen <i>et al</i> [133]

α -SMA: Alpha-smooth-muscle actin; OS: Oxidative stress; SOD: Superoxide dismutase; GSH: Glutathione; IL: Interleukin; Nrf2: Nuclear factor erythroid 2-related factor; HSC: Hepatic stellate cell.

hepatic fibrosis.

Ginkgo biloba leaf is a popular herb that has been used for centuries for various health benefits[98]. *Ginkgo* contains flavonoids and terpenoids, which are known to have antioxidant and anti-inflammatory properties[45]. These compounds make *ginkgo* a potential treatment option for hepatic fibrosis[99]. *Ginkgo biloba* leaf has the potential therapeutic effect of effectively regulating OS induced by thioacetamide and exerting an effect on thioacetamide-induced hepatic fibrosis[100]. Studies have demonstrated that *Ginkgo biloba* leaf can inhibit HSC activation and reduce collagen deposition in liver tissue by regulating OS pathways[100]. In addition, *Ginkgo biloba* leaf has been found to upregulate the expression of Nrf2, a transcription factor that plays a key role in the cellular response to OS[101]. This suggests that *Ginkgo biloba* leaf may be a promising therapeutic agent for hepatic fibrosis.

Clove basil, also known as *Ocimum gratissimum*, is a species of basil that is native to parts of Africa and Asia[102]. It has been used in traditional medicine to treat a variety of conditions, including liver diseases. Recent studies have demonstrated the potential of clove basil extract in preventing the development of hepatic fibrosis through its antioxidant properties. Clove basil contains high levels of phenolic compounds, such as rosmarinic acid, which have potent antioxidant activity. Studies have shown that the clove basil extract possesses anti-hepatic fibrosis properties by inhibiting serum-induced HSC activation and reducing the expression of α -SMA and Col-a[103]. This effect is attributed to the antioxidant components in the extract, which suppress OS and prevent hepatic fibrosis[103]. Additionally, studies have shown that clove basil extract can maintain levels of ALT and AST, as well as MDA, catalase, and α -SMA levels induced by CCl₄, indicating its ability to protect the liver from oxidative damage and promote healing of hepatic fibrosis [104]. Synthetically, clove basil extract has the potential to be used as a therapeutic agent in the treatment of hepatic fibrosis due to its antioxidant and anti-HSC activation properties. However, further studies are needed to explore its mechanism of action and its potential use in clinical settings.

These findings suggest that single herbal extracts may be a potential treatment option for hepatic fibrosis. However, more research is needed to fully understand their effectiveness and potential side effects. It is important to consult with a healthcare professional before taking any herbal supplements, including clove basil.

TCM FORMULAS

The TCM formula stands out for its multi-component, multi-target, and low adverse reaction properties. It employs syndrome differentiation treatment and holistic therapy to regulate the body functions and status, improves prognosis, and eliminates pathogenic factors without harming healthy ones. As a result, TCM formulas show remarkable potential in preventing and treating hepatic fibrosis. This article presents a summary of TCM formulas (Table 4) which have been

Table 4 Traditional Chinese medicine formulas improve hepatic fibrosis by inhibiting oxidative stress

No.	Traditional Chinese medicine formulas	Composition	Efficacy	Model	Upregulated molecules	Downregulated molecules	Mechanism	Ref.
1	Yin-Chen-Hao-Tang	<i>Artemisia annua</i> L. 18 g, <i>Gardenia jasminoides</i> Ellis 12 g, <i>Rheum palmatum</i> 6 g	Clearing heat and promoting diuresis to relieve dampness and jaundice	Rat		Col-I, α -SMA, TGF- β , HYP, ROS	Alleviating hepatic fibrosis by enhancing antioxidant capacity, reducing ROS levels, suppressing OS, and inhibiting inflammatory response	Lee <i>et al</i> [106], Mountford <i>et al</i> [108], Chen <i>et al</i> [109]
2	Xiaochaihu Tang (XCHT)	Bupleurum root 12 g, <i>Scutellaria baicalensis</i> 9 g, Ginseng 6g, <i>Pinellia ternata</i> 9 g, Roasted Licorice 5 g, Fresh Ginger 9 g, 4 Red Dates	Soothing liver and relieving depression, regulating stomach and lowering qi counterflow, tonifying qi and strengthening spleen, clearing liver and purging fire	Rat	Nrf2, Nqo1, HO-2, GCLC, GCLM	α -SMA, HA, PCIII, LN	Activating the Nrf2 pathway can attenuate OS and further suppress activated HSCs, thereby improving hepatic fibrosis	Li <i>et al</i> [111], Hu <i>et al</i> [112]
3	Fu Zheng Hua Yu Fang	<i>Salvia miltiorrhiza</i> , Fermented <i>Cordyceps sinensis</i> powder, Peach kernel, Pine pollen, <i>Lycopodium clavatum</i> , <i>Schisandra chinensis</i> (processed)	Activating blood circulation and removing blood stasis, nourishing essence and nurturing liver	Mice		α -SMA, Nqo1, HO-2, GCLC, GCLM, TIMP1, TGF- β 1, TGF-RI, PDGF-R β , MDA, Col-1a1, TGF- β RI, PDGF- β , MCP-1, MIP-1 mRNA	Effectively suppressing the production of liver ROS, inhibiting OS, and exerting anti-fibrotic effects	Jiang <i>et al</i> [116]
4	CGX	<i>Artemisia annua</i> 5g, <i>Trionyx sinensis</i> shell 5g, Radish seed 5g; White Atractylodes 3g, Pogostemon cablin 3g, <i>Alisma orientale</i> 3g, White Atractylodes 3g, <i>Salvia miltiorrhiza</i> 3g; <i>Poria cocos</i> 2g, Aurantium fruit 2g, Amomum cardamomum 2g, Licorice 1g, <i>Saussurea costus</i> 1g	Clearing liver and activating blood circulation, strengthening spleen and transforming dampness	Rat	GSH-Px, GSH-Rd, GST, SOD, IFN- γ	MDA, PDGF-BB, TGF- β 1, CTGF	It inhibits the levels of liver tissue HYP and MDA, while increasing the total GSH content and the activity of GSH-oxidation reduction system enzymes, which suppresses OS and exerts its anti-hepatic fibrosis effects	Kim <i>et al</i> [134]
5	Huangjia Ruangan Granule	<i>Astragalus membranaceus</i> , <i>Trionyx sinensis</i> shell, <i>Pueraria lobata</i> root, Bupleurum root, <i>Ganoderma lucidum</i> , <i>Paeonia lactiflora</i> , <i>Salvia miltiorrhiza</i> , <i>Panax notoginseng</i> , <i>Lycopodium clavatum</i> , <i>Phyllanthus urinaria</i>	Regulating qi and soothing liver, activating blood circulation and relieving hardness	Rat	SOD, GSH	PC-III, Col-IV, LN, HA, α -SMA, MDA, MPO, TNF- α , IL-1 β , IL-6, Cox-2, iNOS, TNFR1, p-IkB α , p-P65/P65, p-ERK/ERK, p-JNK/JNK, MAPK p-P38/P38	Antagonizing OS effectively inhibits hepatic fibrosis by regulating TNF/MAPK and NF- κ B signaling pathways to suppress liver inflammation	Cai <i>et al</i> [135]

α -SMA: Alpha-smooth-muscle actin; OS: Oxidative stress; SOD: Superoxide dismutase; GSH: Glutathione; IL: Interleukin; IFN: Interferon; Nrf2: Nuclear factor erythroid 2-related factor; HSC: Hepatic stellate cell.

reported to prevent and improve hepatic fibrosis by inhibiting OS.

YCHT is a TCM formula that has been used for centuries to treat liver diseases[105]. It is composed of three herbs, *Artemisia annua* L. (Qing Hao), *Gardenia jasminoides* Ellis (Zhi Zi), and *Rheum palmatum* L. (Da Huang), and is commonly used in clinics in China and other Asian countries[105]. Studies have suggested that YCHT can decrease ROS production and alleviate hepatic fibrosis. One of the mechanisms by which YCHT works is by regulating the balance between the pro- and anti-inflammatory cytokines in the liver[106]. Inflammatory cytokines such as TNF- α , interleukin (IL)-6, and IL-1 β are known to promote ROS production and hepatic fibrosis[107]. YCHT inhibits the expression of these cytokines and promotes the secretion of anti-inflammatory cytokines such as TGF- β and IL-10, which can reduce ROS production and hepatic fibrosis[108]. Another mechanism by which YCHT inhibits ROS production is by increasing the expression of antioxidant enzymes, such as SOD[109]. SOD converts superoxide radicals, one of the primary ROS, into hydrogen peroxide, which is less toxic. This conversion reduces OS in the liver and improves liver function[109]. In short, the

beneficial effects of YCHT on hepatic fibrosis may be attributed to its antioxidant properties. Further studies are needed to fully elucidate the underlying mechanisms and to establish its clinical efficacy and safety for the treatment of hepatic fibrosis.

XCHT is a TCM formula that has been used for centuries to alleviate various ailments, including hepatic fibrosis[110]. Recent studies have shown that XCHT may effectively reduce hepatic fibrosis by inhibiting ROS and OS pathways. Recent research has suggested that XCHT can suppress the production of ROS and reduce OS, leading to improvement in antioxidant capacity[111]. XCHT contains various active compounds such as baicalin, baicalein, and saikosaponin[111]. These compounds have all been shown to possess potent antioxidant properties, which may help to explain XCHT's ability to reduce oxidative liver damage and improve hepatic fibrosis[111]. Furthermore, XCHT has shown promising results in treating hepatic fibrosis by increasing levels of Nqo1, HO-2, GCLC, and GCLM - key components of the Nrf2 pathway in the liver[111]. This mechanism of action is likely responsible for its effectiveness in improving hepatic fibrosis. XCHT has been found to upregulate OS through the Nrf2 pathway, while also inhibiting the proliferation and activation of HSC6 cells, which contributes to its ability to improve hepatic fibrosis[112]. To put it briefly, XCHT has shown promise in reducing hepatic fibrosis by inhibiting ROS and OS pathways, enhancing antioxidant capacity, and modulating the immune system and ECM remodeling processes. Further research is needed to fully understand the molecular mechanisms underlying XCHT's therapeutic effects in hepatic fibrosis and to optimize its clinical application in treating hepatic fibrosis.

Fuzheng Huayu Fang is a formula used in TCM for treating liver diseases and related complications[113]. This formula aims to strengthen the body's immune system, promote blood circulation, and reduce inflammation, hence helping to alleviate the symptoms associated with liver disorders[114]. Fuzheng Huayu Fang contains several herbs with antioxidant and anti-inflammatory properties that help to regulate ROS levels and protect liver cells from damage[115]. For instance, the herb Danshen (*Salvia miltiorrhiza*) has been shown to reduce ROS levels and inhibit the production of pro-inflammatory cytokines in liver cells, thereby improving liver function and reducing hepatic fibrosis[96]. Moreover, some studies have found that Fuzheng Huayu Fang can also help to lower OS and inflammation by regulating the expression of genes involved in these processes[116]. To cut a long story short, Fuzheng Huayu Fang is a useful formula for treating hepatic fibrosis due to its antioxidant and anti-inflammatory properties. By reducing ROS levels and promoting liver regeneration, this formula can help to alleviate the symptoms associated with liver disorders and improve the overall health of the liver.

In essence, TCM formulas have shown great potential in preventing and treating hepatic fibrosis. These formulas can regulate the body's functions and status and improve prognosis without causing adverse reactions. The mechanisms underlying their anti-fibrotic effects involve the suppression of ROS production, inhibition of HSC activation, and regulation of cytokine expression. Further studies are needed to validate their efficacy and safety in clinical practice.

DISCUSSION

Hepatic fibrosis is a compensatory response to liver injury and is also a risk factor for liver cirrhosis, liver cancer, and liver failure. Although the pathogenesis of hepatic fibrosis is complex and not fully understood, OS has been shown to play an important role in the development of hepatic fibrosis diseases. Therefore, the inhibition of OS can prevent hepatic fibrosis and related liver diseases. TCM is a treasure of Chinese traditional medicine, with unique advantages and profound connotations. TCM monomers, single herb extracts, and TCM formulas are increasingly being studied by researchers for their low adverse reactions, cost-effectiveness, and broad targeting of multiple pathways in the prevention and treatment of hepatic fibrosis. Based on the development of modern scientific technologies such as pharmacology and genomics, TCM monomers, single herb extracts, and TCM formulas have been extensively studied for their molecular mechanisms of anti-hepatic fibrosis by targeting OS and intracellular signal transduction processes, achieving good results and having broad application prospects.

However, there are also some issues that need to be addressed at present: Clinical trials are still lacking, and current studies on the role of TCM monomers, single herb extracts, and TCM formulas in inhibiting OS to treat hepatic fibrosis are mainly focused on animal experiments, with limited large-scale clinical trials, which limits the further research and transformation of these TCM monomers, single herb extracts, and TCM formulas. Therefore, how to apply the results of basic experiments to clinical practice and verify the anti-fibrosis effects of TCM monomers, single herb extracts, and TCM formulas in large-scale clinical trials has become another challenge in the treatment of hepatic fibrosis.

In addition, the structure-activity relationship study is not sufficient. Since most polysaccharides, single herb extracts, and TCM formulas are mixtures, their pharmacological mechanisms are difficult to fully elucidate, and they may be limited to the accumulation of effective components of single herb extracts or may be the result of the formation of a systemic pharmacological mechanism of mixtures. This limits the practical application of these TCM in clinical practice. Therefore, TCM theory should be combined with modern medical theory. Based on the summary of previous research, individual differences in pathogenesis and disease progression should be analyzed to further explore how TCM inhibits OS to address hepatic fibrosis.

As well as, some people may be allergic to certain TCMs. If symptoms such as rash, itching, difficulty breathing, or throat swelling occur, medication should be immediately discontinued and medical help should be sought. Additionally, individuals with pre-existing health conditions or those taking other medications should consult healthcare professionals before starting any TCM treatment. This is crucial to ensure the absence of potential drug interactions or worsening of current health issues. Besides, it is important to purchase Chinese medicine products from reputable suppliers to ensure their quality and safety. Counterfeit or adulterated products can pose serious health risks and should be avoided. In

summary, while TCM can provide therapeutic benefits, understanding and addressing potential adverse reactions and preventive measures associated with its use are crucial. By following proper guidelines, consulting healthcare professionals, and using legitimate products, risks can be minimized and benefits can be maximized. This will help find better inducing effects, with fewer adverse reactions and lower prices for TCM, providing a more reliable theoretical basis for achieving true and effective reversal of hepatic fibrosis.

CONCLUSION

Hepatic fibrosis is a condition characterized by inflammation and excessive growth of fibrous tissue in the liver, resulting from long-term exposure to harmful factors. OS is considered a key mechanism in the development and progression of hepatic fibrosis. TCM monomers, single herb extracts, and TCM formulas play important roles in treating hepatic fibrosis by inhibiting OS. This review summarizes the role and effectiveness of TCM monomers, single herb extracts, and TCM formulas in inhibiting OS for the treatment of hepatic fibrosis, based on relevant research. The findings demonstrate that TCM monomers, single herb extracts, and TCM formulas possess significant antioxidant properties, effectively reducing OS levels in the liver and alleviating the occurrence and progression of hepatic fibrosis.

FOOTNOTES

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REFERENCES

- 1 He Z, Yang DY, Fan XL, Zhang MWW, Li Y, Gu XB, Yang MY. The Roles and Mechanisms of lncRNAs in Liver Fibrosis. *Int J Mol Sci* 2020; **21**: 1482 [DOI: [10.3390/ijms21041482](https://doi.org/10.3390/ijms21041482)]
- 2 Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 37-49 [PMID: [36258033](https://pubmed.ncbi.nlm.nih.gov/36258033/) DOI: [10.1038/s41575-022-00688-6](https://doi.org/10.1038/s41575-022-00688-6)]
- 3 Xie R, Xiao M, Li L, Ma N, Liu M, Huang X, Liu Q, Zhang Y. Association between SII and hepatic steatosis and liver fibrosis: A population-based study. *Front Immunol* 2022; **13**: 925690 [PMID: [36189280](https://pubmed.ncbi.nlm.nih.gov/36189280/) DOI: [10.3389/fimmu.2022.925690](https://doi.org/10.3389/fimmu.2022.925690)]
- 4 Atta HM. Reversibility and heritability of liver fibrosis: Implications for research and therapy. *World J Gastroenterol* 2015; **21**: 5138-5148 [PMID: [25954087](https://pubmed.ncbi.nlm.nih.gov/25954087/) DOI: [10.3748/wjg.v21.i17.5138](https://doi.org/10.3748/wjg.v21.i17.5138)]
- 5 Zhang D, Zhang Y, Sun B. The Molecular Mechanisms of Liver Fibrosis and Its Potential Therapy in Application. *Int J Mol Sci* 2022; **23** [PMID: [36293428](https://pubmed.ncbi.nlm.nih.gov/36293428/) DOI: [10.3390/ijms232012572](https://doi.org/10.3390/ijms232012572)]
- 6 Wei C, Qiu J, Wu Y, Chen Z, Yu Z, Huang Z, Yang K, Hu H, Liu F. Promising traditional Chinese medicine for the treatment of cholestatic liver disease process (cholestasis, hepatitis, liver fibrosis, liver cirrhosis). *J Ethnopharmacol* 2022; **297**: 115550 [PMID: [35863612](https://pubmed.ncbi.nlm.nih.gov/35863612/) DOI: [10.1016/j.jep.2022.115550](https://doi.org/10.1016/j.jep.2022.115550)]
- 7 Sonoda S, Murata S, Yamaza H, Yuniartha R, Fujiyoshi J, Yoshimaru K, Matsuura T, Oda Y, Ohga S, Tajiri T, Taguchi T, Yamaza T. Targeting hepatic oxidative stress rescues bone loss in liver fibrosis. *Mol Metab* 2022; **66**: 101599 [PMID: [36113772](https://pubmed.ncbi.nlm.nih.gov/36113772/) DOI: [10.1016/j.molmet.2022.101599](https://doi.org/10.1016/j.molmet.2022.101599)]

- 8 **Karsdal MA**, Hjuler ST, Luo Y, Rasmussen DGK, Nielsen MJ, Holm Nielsen S, Leeming DJ, Goodman Z, Arch RH, Patel K, Schuppan D. Assessment of liver fibrosis progression and regression by a serological collagen turnover profile. *Am J Physiol Gastrointest Liver Physiol* 2019; **316**: G25-G31 [PMID: 30160980 DOI: 10.1152/ajpgi.00158.2018]
- 9 **Chen L**, Brenner DA, Kisseleva T. Combatting Fibrosis: Exosome-Based Therapies in the Regression of Liver Fibrosis. *Hepatology* 2019; **3**: 180-192 [PMID: 30766956 DOI: 10.1002/hep4.1290]
- 10 **Poillil Surendran S**, George Thomas R, Moon MJ, Jeong YY. Nanoparticles for the treatment of liver fibrosis. *Int J Nanomedicine* 2017; **12**: 6997-7006 [PMID: 29033567 DOI: 10.2147/IJN.S145951]
- 11 **Eulenberg VM**, Lidbury JA. Hepatic Fibrosis in Dogs. *J Vet Intern Med* 2018; **32**: 26-41 [PMID: 29194760 DOI: 10.1111/jvim.14891]
- 12 **Xu F**, Liu C, Zhou D, Zhang L. TGF- β /SMAD Pathway and Its Regulation in Hepatic Fibrosis. *J Histochem Cytochem* 2016; **64**: 157-167 [PMID: 26747705 DOI: 10.1369/0022155415627681]
- 13 **Ambrosini YM**, Piedra-Mora C, Jennings S, Webster CRL. Serum 25-hydroxyvitamin D and C-reactive protein and plasma von Willebrand concentrations in 23 dogs with chronic hepatopathies. *J Vet Intern Med* 2022; **36**: 966-975 [PMID: 35420222 DOI: 10.1111/jvim.16424]
- 14 **Crosas-Molist E**, Fabregat I. Role of NADPH oxidases in the redox biology of liver fibrosis. *Redox Biol* 2015; **6**: 106-111 [PMID: 26204504 DOI: 10.1016/j.redox.2015.07.005]
- 15 **Dong Z**, Li S, Wang X, Si L, Ma R, Bao L, Bo A. lncRNA GAS5 restrains CCl₄-induced hepatic fibrosis by targeting miR-23a through the PTEN/PI3K/Akt signaling pathway. *Am J Physiol Gastrointest Liver Physiol* 2019; **316**: G539-G550 [PMID: 30735452 DOI: 10.1152/ajpgi.00249.2018]
- 16 **Heo MJ**, Yun J, Kim SG. Role of non-coding RNAs in liver disease progression to hepatocellular carcinoma. *Arch Pharm Res* 2019; **42**: 48-62 [PMID: 30610616 DOI: 10.1007/s12272-018-01104-x]
- 17 **Wei L**, Wang X, Lv L, Liu J, Xing H, Song Y, Xie M, Lei T, Zhang N, Yang M. The emerging role of microRNAs and long noncoding RNAs in drug resistance of hepatocellular carcinoma. *Mol Cancer* 2019; **18**: 147 [PMID: 31651347 DOI: 10.1186/s12943-019-1086-z]
- 18 **George J**, Tsuchishima M, Tsutsumi M. Molecular mechanisms in the pathogenesis of N-nitrosodimethylamine induced hepatic fibrosis. *Cell Death Dis* 2019; **10**: 18 [PMID: 30622238 DOI: 10.1038/s41419-018-1272-8]
- 19 **Hong SW**, Jung KH, Lee HS, Zheng HM, Choi MJ, Lee C, Hong SS. Suppression by fucoidan of liver fibrogenesis via the TGF- β /Smad pathway in protecting against oxidative stress. *Biosci Biotechnol Biochem* 2011; **75**: 833-840 [PMID: 21597183 DOI: 10.1271/bbb.100599]
- 20 **Xiang M**, Lu Y, Xin L, Gao J, Shang C, Jiang Z, Lin H, Fang X, Qu Y, Wang Y, Shen Z, Zhao M, Cui X. Role of Oxidative Stress in Reperfusion following Myocardial Ischemia and Its Treatments. *Oxid Med Cell Longev* 2021; **2021**: 6614009 [PMID: 34055195 DOI: 10.1155/2021/6614009]
- 21 **Ping Z**, Peng Y, Lang H, Xinyong C, Zhiyi Z, Xiaocheng W, Hong Z, Liang S. Oxidative Stress in Radiation-Induced Cardiotoxicity. *Oxid Med Cell Longev* 2020; **2020**: 3579143 [PMID: 32190171 DOI: 10.1155/2020/3579143]
- 22 **Taleb A**, Ahmad KA, Ihsan AU, Qu J, Lin N, Hezam K, Koju N, Hui L, Qilong D. Antioxidant effects and mechanism of silymarin in oxidative stress induced cardiovascular diseases. *Biomed Pharmacother* 2018; **102**: 689-698 [PMID: 29604588 DOI: 10.1016/j.biopha.2018.03.140]
- 23 **Kong D**, Zhang Z, Chen L, Huang W, Zhang F, Wang L, Wang Y, Cao P, Zheng S. Curcumin blunts epithelial-mesenchymal transition of hepatocytes to alleviate hepatic fibrosis through regulating oxidative stress and autophagy. *Redox Biol* 2020; **36**: 101600 [PMID: 32526690 DOI: 10.1016/j.redox.2020.101600]
- 24 **Sadasivam N**, Kim YJ, Radhakrishnan K, Kim DK. Oxidative Stress, Genomic Integrity, and Liver Diseases. *Molecules* 2022; **27** [PMID: 35630636 DOI: 10.3390/molecules27103159]
- 25 **Lee KS**, Buck M, Houghlum K, Chojkier M. Activation of hepatic stellate cells by TGF α and collagen type I is mediated by oxidative stress through c-myc expression. *J Clin Invest* 1995; **96**: 2461-8 [PMID: 7593635 DOI: 10.1172/JCI118304]
- 26 **Arroyave-Ospina JC**, Wu Z, Geng Y, Moshage H. Role of Oxidative Stress in the Pathogenesis of Non-Alcoholic Fatty Liver Disease: Implications for Prevention and Therapy. *Antioxidants (Basel)* 2021; **10** [PMID: 33530432 DOI: 10.3390/antiox10020174]
- 27 **Gu J**, Chen C, Wang J, Chen T, Yao W, Yan T, Liu Z. Withaferin A Exerts Preventive Effect on Liver Fibrosis through Oxidative Stress Inhibition in a Sirtuin 3-Dependent Manner. *Oxid Med Cell Longev* 2020; **2020**: 2452848 [PMID: 33029279 DOI: 10.1155/2020/2452848]
- 28 **Huang W**, Zheng Y, Feng H, Ni L, Ruan YF, Zou XX, Ye M, Zou SQ. Total phenolic extract of *Euscaphis konishii* Hayata Pericarp attenuates carbon tetrachloride (CCl₄)-induced liver fibrosis in mice. *Biomed Pharmacother* 2020; **125**: 109932 [PMID: 32036214 DOI: 10.1016/j.biopha.2020.109932]
- 29 **Di Paola R**, Modafferi S, Siracusa R, Cordaro M, D'Amico R, Ontario ML, Interdonato L, Salinaro AT, Fusco R, Impellizzeri D, Calabrese V, Cuzzocrea S. S-Acetyl-Glutathione Attenuates Carbon Tetrachloride-Induced Liver Injury by Modulating Oxidative Imbalance and Inflammation. *Int J Mol Sci* 2022; **23** [PMID: 35457246 DOI: 10.3390/ijms23084429]
- 30 **Gao YT**, Pan HW, Wu SB. Gross conception of anatomical structure of zang-fu viscera in Huangdi Neijing. *Zhong Xi Yi Jie He Xue Bao* 2006; **4**: 339-342 [PMID: 16834967 DOI: 10.3736/jcim20060404]
- 31 **Jaimes PN**, Reyes AM, Lara DG, Coyuca ACP. Correlation Between the Sinew Channels with the Myofascial System, Pathology, and Treatment. *J Acupunct Meridian Stud* 2022; **15**: 201-213 [PMID: 36521769 DOI: 10.51507/j.jams.2022.15.4.201]
- 32 **Byoung-Hee L**, Min-Yong K, Young-Bae P, Young-Jae P. Development of a valid and reliable seven emotions impairment questionnaire and assessment of its predictability for phlegm and blood stasis. *J Tradit Chin Med* 2016; **36**: 547-554 [PMID: 28459523 DOI: 10.1016/s0254-6272(16)30073-5]
- 33 **Ge C**, Tan J, Lou D, Zhu L, Zhong Z, Dai X, Sun Y, Kuang Q, Zhao J, Wang L, Liu J, Wang B, Xu M. Mulberrin confers protection against hepatic fibrosis by Trim31/Nrf2 signaling. *Redox Biol* 2022; **51**: 102274 [PMID: 35240537 DOI: 10.1016/j.redox.2022.102274]
- 34 **Xiao J**, Muzashvili TS, Georgiev MI. Advances in the biotechnological glycosylation of valuable flavonoids. *Biotechnol Adv* 2014; **32**: 1145-1156 [PMID: 24780153 DOI: 10.1016/j.biotechadv.2014.04.006]
- 35 **Parhiz H**, Roohbakhsh A, Soltani F, Rezaee R, Iranshahi M. Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models. *Phytother Res* 2015; **29**: 323-331 [PMID: 25394264 DOI: 10.1002/ptr.5256]
- 36 **Maleki SJ**, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. *Food Chem* 2019; **299**: 125124 [PMID: 31288163 DOI: 10.1016/j.foodchem.2019.125124]
- 37 **Ma M**, Duan R, Zhong H, Liang T, Guo L. The Crosstalk between Fat Homeostasis and Liver Regional Immunity in NAFLD. *J Immunol Res* 2019; **2019**: 3954890 [PMID: 30719457 DOI: 10.1155/2019/3954890]

- 38 Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and metabolic syndrome: A review. *Phytother Res* 2021; **35**: 5352-5364 [PMID: 34101925 DOI: 10.1002/ptr.7144]
- 39 Patel RV, Mistry BM, Shinde SK, Syed R, Singh V, Shin HS. Therapeutic potential of quercetin as a cardiovascular agent. *Eur J Med Chem* 2018; **155**: 889-904 [PMID: 29966915 DOI: 10.1016/j.ejmech.2018.06.053]
- 40 Alizadeh SR, Ebrahimzadeh MA. Quercetin derivatives: Drug design, development, and biological activities, a review. *Eur J Med Chem* 2022; **229**: 114068 [PMID: 34971873 DOI: 10.1016/j.ejmech.2021.114068]
- 41 Dabeek WM, Marra MV. Dietary Quercetin and Kaempferol: Bioavailability and Potential Cardiovascular-Related Bioactivity in Humans. *Nutrients* 2019; **11** [PMID: 31557798 DOI: 10.3390/nu11102288]
- 42 Shen P, Lin W, Deng X, Ba X, Han L, Chen Z, Qin K, Huang Y, Tu S. Potential Implications of Quercetin in Autoimmune Diseases. *Front Immunol* 2021; **12**: 689044 [PMID: 34248976 DOI: 10.3389/fimmu.2021.689044]
- 43 Aslam A, Sheikh N, Shahzad M, Saeed G, Fatima N, Akhtar T. Quercetin ameliorates thioacetamide-induced hepatic fibrosis and oxidative stress by antagonizing the Hedgehog signaling pathway. *J Cell Biochem* 2022; **123**: 1356-1365 [PMID: 35696520 DOI: 10.1002/jcb.30296]
- 44 Khodarahmi A, Eshaghian A, Safari F, Moradi A. Quercetin Mitigates Hepatic Insulin Resistance in Rats with Bile Duct Ligation Through Modulation of the STAT3/SOCS3/IRS1 Signaling Pathway. *J Food Sci* 2019; **84**: 3045-3053 [PMID: 31529802 DOI: 10.1111/1750-3841.14793]
- 45 Gong G, Guan YY, Zhang ZL, Rahman K, Wang SJ, Zhou S, Luan X, Zhang H. Isorhamnetin: A review of pharmacological effects. *Biomed Pharmacother* 2020; **128**: 110301 [PMID: 32502837 DOI: 10.1016/j.biopha.2020.110301]
- 46 Hu J, Zhang Y, Jiang X, Zhang H, Gao Z, Li Y, Fu R, Li L, Li J, Cui H, Gao N. ROS-mediated activation and mitochondrial translocation of CaMKII contributes to Drp1-dependent mitochondrial fission and apoptosis in triple-negative breast cancer cells by isorhamnetin and chloroquine. *J Exp Clin Cancer Res* 2019; **38**: 225 [PMID: 31138329 DOI: 10.1186/s13046-019-1201-4]
- 47 Li X, Chen H, Zhang Z, Xu D, Duan J, Li X, Yang L, Hua R, Cheng J, Li Q. Isorhamnetin Promotes Estrogen Biosynthesis and Proliferation in Porcine Granulosa Cells via the PI3K/Akt Signaling Pathway. *J Agric Food Chem* 2021; **69**: 6535-6542 [PMID: 34096286 DOI: 10.1021/acs.jafc.1c01543]
- 48 Kalai FZ, Boulaaba M, Ferdousi F, Isoda H. Effects of Isorhamnetin on Diabetes and Its Associated Complications: A Review of In Vitro and In Vivo Studies and a Post Hoc Transcriptome Analysis of Involved Molecular Pathways. *Int J Mol Sci* 2022; **23** [PMID: 35054888 DOI: 10.3390/ijms23020704]
- 49 Yang JH, Kim SC, Kim KM, Jang CH, Cho SS, Kim SJ, Ku SK, Cho IJ, Ki SH. Isorhamnetin attenuates liver fibrosis by inhibiting TGF- β /Smad signaling and relieving oxidative stress. *Eur J Pharmacol* 2016; **783**: 92-102 [PMID: 27151496 DOI: 10.1016/j.ejphar.2016.04.042]
- 50 Chen R, Qi QL, Wang MT, Li QY. Therapeutic potential of naringin: an overview. *Pharm Biol* 2016; **54**: 3203-3210 [PMID: 27564838 DOI: 10.1080/13880209.2016.1216131]
- 51 Zeng W, Jin L, Zhang F, Zhang C, Liang W. Naringenin as a potential immunomodulator in therapeutics. *Pharmacol Res* 2018; **135**: 122-126 [PMID: 30081177 DOI: 10.1016/j.phrs.2018.08.002]
- 52 Hernández-Aquino E, Muriel P. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. *World J Gastroenterol* 2018; **24**: 1679-1707 [PMID: 29713125 DOI: 10.3748/wjg.v24.i16.1679]
- 53 Hernández-Aquino E, Zarco N, Casas-Grajales S, Ramos-Tovar E, Flores-Beltrán RE, Arauz J, Shibayama M, Favari L, Tsutsumi V, Segovia J, Muriel P. Naringenin prevents experimental liver fibrosis by blocking TGF β -Smad3 and JNK-Smad3 pathways. *World J Gastroenterol* 2017; **23**: 4354-4368 [PMID: 28706418 DOI: 10.3748/wjg.v23.i24.4354]
- 54 Hernández-Aquino E, Quezada-Ramírez MA, Silva-Olivares A, Casas-Grajales S, Ramos-Tovar E, Flores-Beltrán RE, Segovia J, Shibayama M, Muriel P. Naringenin attenuates the progression of liver fibrosis via inactivation of hepatic stellate cells and profibrogenic pathways. *Eur J Pharmacol* 2019; **865**: 172730 [PMID: 31618621 DOI: 10.1016/j.ejphar.2019.172730]
- 55 Kren V, Martinková L. Glycosides in medicine: "The role of glycosidic residue in biological activity". *Curr Med Chem* 2001; **8**: 1303-1328 [PMID: 11562268 DOI: 10.2174/0929867013372193]
- 56 Zou Y, Fang W. Naturally Derived Glycosides with Potential Activity against Staphylococcus Aureus. *Curr Top Med Chem* 2021; **21**: 2500-2512 [PMID: 34649487 DOI: 10.2174/1568026621666211015091539]
- 57 Fan J, Li X, Li P, Li N, Wang T, Shen H, Siow Y, Choy P, Gong Y. Saikosaponin-d attenuates the development of liver fibrosis by preventing hepatocyte injury. *Biochem Cell Biol* 2007; **85**: 189-195 [PMID: 17534399 DOI: 10.1139/O07-010]
- 58 Manoharan S, Deivendran B, Perumal E. Chemotherapeutic Potential of Saikosaponin D: Experimental Evidence. *J Xenobiot* 2022; **12**: 378-405 [PMID: 36547471 DOI: 10.3390/jox12040027]
- 59 Li X, Li X, Huang N, Liu R, Sun R. A comprehensive review and perspectives on pharmacology and toxicology of saikosaponins. *Phytomedicine* 2018; **50**: 73-87 [PMID: 30466994 DOI: 10.1016/j.phymed.2018.09.174]
- 60 Que R, Shen Y, Ren J, Tao Z, Zhu X, Li Y. Estrogen receptor β -dependent effects of saikosaponin on the suppression of oxidative stress-induced rat hepatic stellate cell activation. *Int J Mol Med* 2018; **41**: 1357-1364 [PMID: 29286085 DOI: 10.3892/ijmm.2017.3349]
- 61 Weiskirchen S, Weiskirchen R. Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy? *Adv Nutr* 2016; **7**: 706-718 [PMID: 27422505 DOI: 10.3945/an.115.011627]
- 62 Pandey RP, Parajuli P, Shin JY, Lee J, Lee S, Hong YS, Park YI, Kim JS, Sohng JK. Enzymatic Biosynthesis of Novel Resveratrol Glucoside and Glycoside Derivatives. *Appl Environ Microbiol* 2014; **80**: 7235-7243 [PMID: 25239890 DOI: 10.1128/AEM.02076-14]
- 63 Tong J, Gao J, Liu Q, He C, Zhao X, Qi Y, Yuan T, Li P, Niu M, Wang D, Zhang L, Li W, Wang J, Zhang Z, Peng S. Resveratrol derivative excited postsynaptic potentiation specifically via PKC β -NMDA receptor mediation. *Pharmacol Res* 2020; **152**: 104618 [PMID: 31891789 DOI: 10.1016/j.phrs.2019.104618]
- 64 Jang IA, Kim EN, Lim JH, Kim MY, Ban TH, Yoon HE, Park CW, Chang YS, Choi BS. Effects of Resveratrol on the Renin-Angiotensin System in the Aging Kidney. *Nutrients* 2018; **10** [PMID: 30424556 DOI: 10.3390/nu10111741]
- 65 Ding KN, Lu MH, Guo YN, Liang SS, Mou RW, He YM, Tang LP. Resveratrol relieves chronic heat stress-induced liver oxidative damage in broilers by activating the Nrf2-Keap1 signaling pathway. *Ecotoxicol Environ Saf* 2023; **249**: 114411 [PMID: 36525949 DOI: 10.1016/j.ecoenv.2022.114411]
- 66 Yu B, Qin SY, Hu BL, Qin QY, Jiang HX, Luo W. Resveratrol improves CCL4-induced liver fibrosis in mouse by upregulating endogenous IL-10 to reprogramme macrophages phenotype from M(LPS) to M(IL-4). *Biomed Pharmacother* 2019; **117**: 109110 [PMID: 31252263 DOI: 10.1016/j.biopha.2019.109110]
- 67 Wang Y, Wu H, Gui BJ, Liu J, Rong GX, Deng R, Bu YH, Zhang H. Geniposide alleviates VEGF-induced angiogenesis by inhibiting VEGFR2/PKC/ERK1/2-mediated SphK1 translocation. *Phytomedicine* 2022; **100**: 154068 [PMID: 35358930 DOI: 10.1016/j.phymed.2022.100154068]

- 10.1016/j.phymed.2022.154068]
- 68 **Jin Z**, Li J, Pi J, Chu Q, Wei W, Du Z, Qing L, Zhao X, Wu W. Geniposide alleviates atherosclerosis by regulating macrophage polarization via the FOS/MAPK signaling pathway. *Biomed Pharmacother* 2020; **125**: 110015 [PMID: 32187958 DOI: 10.1016/j.biopha.2020.110015]
- 69 **Wen M**, Liu Y, Chen R, He P, Wu F, Li R, Lin Y. Geniposide suppresses liver injury in a mouse model of DDC-induced sclerosing cholangitis. *Phytother Res* 2021; **35**: 3799-3811 [PMID: 33763888 DOI: 10.1002/ptr.7086]
- 70 **Yang L**, Bi L, Jin L, Wang Y, Li Y, Li Z, He W, Cui H, Miao J, Wang L. Geniposide Ameliorates Liver Fibrosis Through Reducing Oxidative Stress and Inflammatory Respose, Inhibiting Apoptosis and Modulating Overall Metabolism. *Front Pharmacol* 2021; **12**: 772635 [PMID: 34899328 DOI: 10.3389/fphar.2021.772635]
- 71 **Ziegler J**, Facchini PJ. Alkaloid biosynthesis: metabolism and trafficking. *Annu Rev Plant Biol* 2008; **59**: 735-769 [PMID: 18251710 DOI: 10.1146/annurev.arplant.59.032607.092730]
- 72 **Bhambhani S**, Kondhare KR, Giri AP. Diversity in Chemical Structures and Biological Properties of Plant Alkaloids. *Molecules* 2021; **26** [PMID: 34204857 DOI: 10.3390/molecules26113374]
- 73 **Feng X**, Sureda A, Jafari S, Memariani Z, Tewari D, Annunziata G, Barrea L, Hassan STS, Šmejkal K, Malanik M, Sychrová A, Barreca D, Ziberna L, Mahomoodally MF, Zengin G, Xu S, Nabavi SM, Shen AZ. Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics. *Theranostics* 2019; **9**: 1923-1951 [PMID: 31037148 DOI: 10.7150/thno.30787]
- 74 **Habtemariam S**. Berberine pharmacology and the gut microbiota: A hidden therapeutic link. *Pharmacol Res* 2020; **155**: 104722 [PMID: 32105754 DOI: 10.1016/j.phrs.2020.104722]
- 75 **Eissa LA**, Kenawy HI, El-Karef A, Elsherbiny NM, El-Mihi KA. Antioxidant and anti-inflammatory activities of berberine attenuate hepatic fibrosis induced by thioacetamide injection in rats. *Chem Biol Interact* 2018; **294**: 91-100 [PMID: 30138605 DOI: 10.1016/j.cbi.2018.08.016]
- 76 **Yi J**, Wu S, Tan S, Qin Y, Wang X, Jiang J, Liu H, Wu B. Berberine alleviates liver fibrosis through inducing ferrous redox to activate ROS-mediated hepatic stellate cells ferroptosis. *Cell Death Discov* 2021; **7**: 374 [PMID: 34864819 DOI: 10.1038/s41420-021-00768-7]
- 77 **Domitrović R**, Jakovac H, Marchesi VV, Blažeković B. Resolution of liver fibrosis by isoquinoline alkaloid berberine in CCl₄-intoxicated mice is mediated by suppression of oxidative stress and upregulation of MMP-2 expression. *J Med Food* 2013; **16**: 518-528 [PMID: 23734997 DOI: 10.1089/jmf.2012.0175]
- 78 **Zhao G**, He F, Wu C, Li P, Li N, Deng J, Zhu G, Ren W, Peng Y. Betaine in Inflammation: Mechanistic Aspects and Applications. *Front Immunol* 2018; **9**: 1070 [PMID: 29881379 DOI: 10.3389/fimmu.2018.01070]
- 79 **Arumugam MK**, Chava S, Perumal SK, Paal MC, Rasineni K, Ganesan M, Donohue TM Jr, Osna NA, Kharbanda KK. Acute ethanol-induced liver injury is prevented by betaine administration. *Front Physiol* 2022; **13**: 940148 [PMID: 36267591 DOI: 10.3389/fphys.2022.940148]
- 80 **Bingül İ**, Başaran-Küçükgergin C, Aydın AF, Çoban J, Doğan-Ekici I, Doğru-Abbasoğlu S, Uysal M. Betaine treatment decreased oxidative stress, inflammation, and stellate cell activation in rats with alcoholic liver fibrosis. *Environ Toxicol Pharmacol* 2016; **45**: 170-178 [PMID: 27314760 DOI: 10.1016/j.etap.2016.05.033]
- 81 **Bingül İ**, Aydın AF, Başaran-Küçükgergin C, Doğan-Ekici I, Çoban J, Doğru-Abbasoğlu S, Uysal M. High-fat diet plus carbon tetrachloride-induced liver fibrosis is alleviated by betaine treatment in rats. *Int Immunopharmacol* 2016; **39**: 199-207 [PMID: 27494683 DOI: 10.1016/j.intimp.2016.07.028]
- 82 **Kim SK**, Seo JM, Chae YR, Jung YS, Park JH, Kim YC. Alleviation of dimethylnitrosamine-induced liver injury and fibrosis by betaine supplementation in rats. *Chem Biol Interact* 2009; **177**: 204-211 [PMID: 18930038 DOI: 10.1016/j.cbi.2008.09.021]
- 83 **Liang Q**, Cai W, Zhao Y, Xu H, Tang H, Chen D, Qian F, Sun L. Lycorine ameliorates bleomycin-induced pulmonary fibrosis via inhibiting NLRP3 inflammasome activation and pyroptosis. *Pharmacol Res* 2020; **158**: 104884 [PMID: 32428667 DOI: 10.1016/j.phrs.2020.104884]
- 84 **Roy M**, Liang L, Xiao X, Feng P, Ye M, Liu J. Lycorine: A prospective natural lead for anticancer drug discovery. *Biomed Pharmacother* 2018; **107**: 615-624 [PMID: 30114645 DOI: 10.1016/j.biopha.2018.07.147]
- 85 **Ilavenil S**, Kaleeswaran B, Ravikumar S. Protective effects of lycorine against carbon tetrachloride induced hepatotoxicity in Swiss albino mice. *Fundam Clin Pharmacol* 2012; **26**: 393-401 [PMID: 21480982 DOI: 10.1111/j.1472-8206.2011.00942.x]
- 86 **Jin M**, Shi J, Zhu W, Yao H, Wang DA. Polysaccharide-Based Biomaterials in Tissue Engineering: A Review. *Tissue Eng Part B Rev* 2021; **27**: 604-626 [PMID: 33267648 DOI: 10.1089/ten.TEB.2020.0208]
- 87 **Yang S**, Yang X, Zhang H. Extracellular polysaccharide biosynthesis in Cordyceps. *Crit Rev Microbiol* 2020; **46**: 359-380 [PMID: 32720528 DOI: 10.1080/1040841X.2020.1794788]
- 88 **Liu Y**, Li Y, Zhang H, Li C, Zhang Z, Liu A, Chen H, Hu B, Luo Q, Lin B, Wu W. Polysaccharides from Cordyceps militaris cultured at different pH: Sugar composition and antioxidant activity. *Int J Biol Macromol* 2020; **162**: 349-358 [PMID: 32574745 DOI: 10.1016/j.ijbiomac.2020.06.182]
- 89 **Peng J**, Li X, Feng Q, Chen L, Xu L, Hu Y. Anti-fibrotic effect of Cordyceps sinensis polysaccharide: Inhibiting HSC activation, TGF-β1/Smad signalling, MMPs and TIMPs. *Exp Biol Med (Maywood)* 2013; **238**: 668-677 [PMID: 23918878 DOI: 10.1177/1535370213480741]
- 90 **Liu Y**, E Q, Zuo J, Tao Y, Liu W. Protective effect of Cordyceps polysaccharide on hydrogen peroxide-induced mitochondrial dysfunction in HL-7702 cells. *Mol Med Rep* 2013; **7**: 747-754 [PMID: 23258306 DOI: 10.3892/mmr.2012.1248]
- 91 **Zhao H**, Li D, Li M, Liu L, Deng B, Jia L, Yang F. Coprinus comatus polysaccharides ameliorated carbon tetrachloride-induced liver fibrosis through modulating inflammation and apoptosis. *Food Funct* 2022; **13**: 11125-11141 [PMID: 36205351 DOI: 10.1039/d2fo01349e]
- 92 **Jia Q**, Zhu R, Tian Y, Chen B, Li R, Li L, Wang L, Che Y, Zhao D, Mo F, Gao S, Zhang D. Salvia miltiorrhiza in diabetes: A review of its pharmacology, phytochemistry, and safety. *Phytomedicine* 2019; **58**: 152871 [PMID: 30851580 DOI: 10.1016/j.phymed.2019.152871]
- 93 **Wang X**, Liu W, Jin G, Wu Z, Zhang D, Bao Y, Shi W. Salvia miltiorrhiza polysaccharides alleviates florfenicol induced kidney injury in chicks via inhibiting oxidative stress and apoptosis. *Ecotoxicol Environ Saf* 2022; **233**: 113339 [PMID: 35219255 DOI: 10.1016/j.ecoenv.2022.113339]
- 94 **Zhang Y**, Zhang Y, Xie Y, Gao Y, Ma J, Yuan J, Li J, Wang J, Li L, Zhang J, Chu L. Multitargeted inhibition of hepatic fibrosis in chronic iron-overloaded mice by Salvia miltiorrhiza. *J Ethnopharmacol* 2013; **148**: 671-681 [PMID: 23707206 DOI: 10.1016/j.jep.2013.05.028]
- 95 **Gao Y**, Wang N, Zhang Y, Ma Z, Guan P, Ma J, Zhang X, Wang J, Zhang J, Chu L. Mechanism of protective effects of Danshen against iron overload-induced injury in mice. *J Ethnopharmacol* 2013; **145**: 254-260 [PMID: 23147497 DOI: 10.1016/j.jep.2012.10.060]
- 96 **Wang R**, Wang J, Song F, Li S, Yuan Y. Tanshinol ameliorates CCl₄-induced liver fibrosis in rats through the regulation of Nrf2/HO-1 and NF-κB/IκBα signaling pathway. *Drug Des Devel Ther* 2018; **12**: 1281-1292 [PMID: 29844659 DOI: 10.2147/DDDT.S159546]
- 97 **Li S**, Wang R, Song F, Chen P, Gu Y, Chen C, Yuan Y. Salvianolic acid A suppresses CCl₄-induced liver fibrosis through regulating the Nrf2/HO-1, NF-κB/IκBα, p38 MAPK, and JAK1/STAT3 signaling pathways. *Drug Chem Toxicol* 2023; **46**: 304-313 [PMID: 35057680 DOI: 10.1080/01480545.2022.2028822]

- 98 Yoshikawa T, Naito Y, Kondo M. Ginkgo biloba leaf extract: review of biological actions and clinical applications. *Antioxid Redox Signal* 1999; **1**: 469-480 [PMID: 11233145 DOI: 10.1089/ars.1999.1.4-469]
- 99 Ding J, Yu J, Wang C, Hu W, Li D, Luo Y, Luo H, Yu H. Ginkgo biloba extract alleviates liver fibrosis induced by CCl₄ in rats. *Liver Int* 2005; **25**: 1224-1232 [PMID: 16343076 DOI: 10.1111/j.1478-3231.2005.01169.x]
- 100 Al-Attar AM. Attenuating effect of Ginkgo biloba leaves extract on liver fibrosis induced by thioacetamide in mice. *J Biomed Biotechnol* 2012; **2012**: 761450 [PMID: 23091357 DOI: 10.1155/2012/761450]
- 101 Jeong HS, Kim KH, Lee IS, Park JY, Kim Y, Kim KS, Jang HJ. Ginkgolide A ameliorates non-alcoholic fatty liver diseases on high fat diet mice. *Biomed Pharmacother* 2017; **88**: 625-634 [PMID: 28142119 DOI: 10.1016/j.biopha.2017.01.114]
- 102 Brum A, Pereira SA, Cardoso L, Chagas EC, Chaves FCM, Mourão JLP, Martins ML. Blood biochemical parameters and melanomacrophage centers in Nile tilapia fed essential oils of clove basil and ginger. *Fish Shellfish Immunol* 2018; **74**: 444-449 [PMID: 29353078 DOI: 10.1016/j.fsi.2018.01.021]
- 103 Chiu YW, Chao PY, Tsai CC, Chiou HL, Liu YC, Hung CC, Shih HC, Lai TJ, Liu JY. Ocimum gratissimum is effective in prevention against liver fibrosis *in vivo* and *in vitro*. *Am J Chin Med* 2014; **42**: 833-852 [PMID: 25004878 DOI: 10.1142/S0192415X14500530]
- 104 Chen YH, Chiu YW, Shyu JC, Tsai CC, Lee HH, Hung CC, Hwang JM, Liu JY, Wang WH. Protective effects of Ocimum gratissimum polyphenol extract on carbon tetrachloride-induced liver fibrosis in rats. *Chin J Physiol* 2015; **58**: 55-63 [PMID: 25687492 DOI: 10.4077/CJP.2015.BAD285]
- 105 Xiang H, Wang G, Qu J, Xia S, Tao X, Qi B, Zhang Q, Shang D. Yin-Chen-Hao Tang Attenuates Severe Acute Pancreatitis in Rat: An Experimental Verification of In silico Network Target Prediction. *Front Pharmacol* 2016; **7**: 378 [PMID: 27790147 DOI: 10.3389/fphar.2016.00378]
- 106 Lee TY, Chang HH, Lo WC, Lin HC. Alleviation of hepatic oxidative stress by Chinese herbal medicine Yin-Chen-Hao-Tang in obese mice with steatosis. *Int J Mol Med* 2010; **25**: 837-844 [PMID: 20428786 DOI: 10.3892/ijmm.00000412]
- 107 Seki E, Brenner DA. Recent advancement of molecular mechanisms of liver fibrosis. *J Hepatobiliary Pancreat Sci* 2015; **22**: 512-518 [PMID: 25869468 DOI: 10.1002/jhbp.245]
- 108 Mountford S, Effenberger M, Noll-Puchta H, Griessmair L, Ringleb A, Haas S, Denk G, Reiter FP, Mayr D, Dinarello CA, Tilg H, Bufler P. Modulation of Liver Inflammation and Fibrosis by Interleukin-37. *Front Immunol* 2021; **12**: 603649 [PMID: 33746950 DOI: 10.3389/fimmu.2021.603649]
- 109 Chen Z, Wang X, Li Y, Wang Y, Tang K, Wu D, Zhao W, Ma Y, Liu P, Cao Z. Comparative Network Pharmacology Analysis of Classical TCM Prescriptions for Chronic Liver Disease. *Front Pharmacol* 2019; **10**: 1353 [PMID: 31824313 DOI: 10.3389/fphar.2019.01353]
- 110 Wang SJ, Ye W, Li WY, Tian W, Zhang M, Sun Y, Feng YD, Liu CX, Liu SY, Cao W, Meng JR, Li XQ. Effects and mechanisms of Xiaochaihu Tang against liver fibrosis: An integration of network pharmacology, molecular docking and experimental validation. *J Ethnopharmacol* 2023; **303**: 116053 [PMID: 36529247 DOI: 10.1016/j.jep.2022.116053]
- 111 Li J, Hu R, Xu S, Li Y, Qin Y, Wu Q, Xiao Z. Xiaochaihutang attenuates liver fibrosis by activation of Nrf2 pathway in rats. *Biomed Pharmacother* 2017; **96**: 847-853 [PMID: 29078262 DOI: 10.1016/j.biopha.2017.10.065]
- 112 Hu R, Jia WY, Xu SF, Zhu ZW, Xiao Z, Yu SY, Li J. Xiaochaihutang Inhibits the Activation of Hepatic Stellate Cell Line T6 Through the Nrf2 Pathway. *Front Pharmacol* 2018; **9**: 1516 [PMID: 30666206 DOI: 10.3389/fphar.2018.01516]
- 113 Sun S, Dai J, Wang W, Cao H, Fang J, Hu YY, Su S, Zhang Y. Metabonomic Evaluation of ZHENG Differentiation and Treatment by Fuzhenghuayu Tablet in Hepatitis-B-Caused Cirrhosis. *Evid Based Complement Alternat Med* 2012; **2012**: 453503 [PMID: 22690245 DOI: 10.1155/2012/453503]
- 114 Chen J, Gao W, Zhou P, Ma X, Tschudy-Seney B, Liu C, Zern MA, Liu P, Duan Y. Enhancement of hepatocyte differentiation from human embryonic stem cells by Chinese medicine Fuzhenghuayu. *Sci Rep* 2016; **6**: 18841 [PMID: 26733102 DOI: 10.1038/srep18841]
- 115 Zhang ZG, Lu XB, Xiao L, Tang L, Zhang LJ, Zhang T, Zhan XY, Ma XM, Zhang YX. Antioxidant effects of the Uygur herb, Foeniculum Vulgare Mill, in a rat model of hepatic fibrosis. *Zhonghua Gan Zang Bing Za Zhi* 2012; **20**: 221-226 [PMID: 22475144 DOI: 10.3760/cma.j.issn.1007-3418.2012.03.017]
- 116 Jiang C, Iwaisako K, Cong M, Diggle K, Hassanein T, Brenner DA, Kisseleva T. Traditional Chinese Medicine Fuzheng Huayu Prevents Development of Liver Fibrosis in Mice. *Arch Clin Biomed Res* 2020; **4**: 561-580 [PMID: 33210080 DOI: 10.26502/acbr.50170125]
- 117 Zhang B, Lai L, Tan Y, Liang Q, Bai F, Mai W, Huang Q, Ye Y. Hepatoprotective effect of total flavonoids of Mallotus apelta (Lour.) Muell.Arg. leaf against carbon tetrachloride-induced liver fibrosis in rats via modulation of TGF- β 1/Smad and NF- κ B signaling pathways. *J Ethnopharmacol* 2020; **254**: 112714 [PMID: 32105750 DOI: 10.1016/j.jep.2020.112714]
- 118 Yuan LP, Chen FH, Ling L, Bo H, Chen ZW, Li F, Zhong MM, Xia LJ. Protective effects of total flavonoids of Bidens bipinnata L. against carbon tetrachloride-induced liver fibrosis in rats. *J Pharm Pharmacol* 2008; **60**: 1393-1402 [PMID: 18812033 DOI: 10.1211/jpp.60.10.0016]
- 119 Hou B, Zhao Y, Qiang G, Yang X, Xu C, Chen X, Liu C, Wang X, Zhang L, Du G. Puerarin Mitigates Diabetic Hepatic Steatosis and Fibrosis by Inhibiting TGF- β Signaling Pathway Activation in Type 2 Diabetic Rats. *Oxid Med Cell Longev* 2018; **2018**: 4545321 [PMID: 30057680 DOI: 10.1155/2018/4545321]
- 120 Li S, Li X, Chen F, Liu M, Ning L, Yan Y, Zhang S, Huang S, Tu C. Nobiletin mitigates hepatocytes death, liver inflammation, and fibrosis in a murine model of NASH through modulating hepatic oxidative stress and mitochondrial dysfunction. *J Nutr Biochem* 2022; **100**: 108888 [PMID: 34695558 DOI: 10.1016/j.jnutbio.2021.108888]
- 121 Zhu Z, Hu R, Li J, Xing X, Chen J, Zhou Q, Sun J. Alpinetin exerts anti-inflammatory, anti-oxidative and anti-angiogenic effects through activating the Nrf2 pathway and inhibiting NLRP3 pathway in carbon tetrachloride-induced liver fibrosis. *Int Immunopharmacol* 2021; **96**: 107660 [PMID: 33862553 DOI: 10.1016/j.intimp.2021.107660]
- 122 El-Fadaly AA, Afifi NA, El-Eraky W, Salama A, Abdelhameed MF, El-Rahman SSA, Ramadan A. Fisetin alleviates thioacetamide-induced hepatic fibrosis in rats by inhibiting Wnt/ β -catenin signaling pathway. *Immunopharmacol Immunotoxicol* 2022; **44**: 355-366 [PMID: 35255766 DOI: 10.1080/08923973.2022.2047198]
- 123 Zhang L, Zhang H, Gu J, Xu W, Yuan N, Sun J, Li H. Glabridin inhibits liver fibrosis and hepatic stellate cells activation through suppression of inflammation and oxidative stress by activating PPAR γ in carbon tetrachloride-treated mice. *Int Immunopharmacol* 2022; **113**: 109433 [PMID: 36371863 DOI: 10.1016/j.intimp.2022.109433]
- 124 Heeba GH, Mahmoud ME. Therapeutic potential of morin against liver fibrosis in rats: modulation of oxidative stress, cytokine production and nuclear factor kappa B. *Environ Toxicol Pharmacol* 2014; **37**: 662-671 [PMID: 24583409 DOI: 10.1016/j.etap.2014.01.026]
- 125 Sun XH, Zhang H, Fan XP, Wang ZH. Astilbin Protects Against Carbon Tetrachloride-Induced Liver Fibrosis in Rats. *Pharmacology* 2021; **106**: 323-331 [PMID: 33780953 DOI: 10.1159/000514594]

- 126 **Wang Q**, Wen R, Lin Q, Wang N, Lu P, Zhu X. Wogonoside Shows Antifibrotic Effects in an Experimental Regression Model of Hepatic Fibrosis. *Dig Dis Sci* 2015; **60**: 3329-3339 [PMID: 26130019 DOI: 10.1007/s10620-015-3751-4]
- 127 **Zou L**, Chen S, Li L, Wu T. The protective effect of hyperoside on carbon tetrachloride-induced chronic liver fibrosis in mice *via* upregulation of Nrf2. *Exp Toxicol Pathol* 2017; **69**: 451-460 [PMID: 28434817 DOI: 10.1016/j.etp.2017.04.001]
- 128 **Fu K**, Ma C, Wang C, Zhou H, Gong L, Zhang Y, Li Y. Forsythiaside A alleviated carbon tetrachloride-induced liver fibrosis by modulating gut microbiota composition to increase short-chain fatty acids and restoring bile acids metabolism disorder. *Biomed Pharmacother* 2022; **151**: 113185 [PMID: 35623173 DOI: 10.1016/j.biopha.2022.113185]
- 129 **Al-Olayan EM**, El-Khadragy MF, Alajmi RA, Othman MS, Bauomy AA, Ibrahim SR, Abdel Moneim AE. Ceratonia siliqua pod extract ameliorates Schistosoma mansoni-induced liver fibrosis and oxidative stress. *BMC Complement Altern Med* 2016; **16**: 434 [PMID: 27821159 DOI: 10.1186/s12906-016-1389-1]
- 130 **Dulundu E**, Ozel Y, Topaloglu U, Toklu H, Ercan F, Gedik N, Sener G. Grape seed extract reduces oxidative stress and fibrosis in experimental biliary obstruction. *J Gastroenterol Hepatol* 2007; **22**: 885-892 [PMID: 17565645 DOI: 10.1111/j.1440-1746.2007.04875.x]
- 131 **Husain H**, Latief U, Ahmad R. Pomegranate action in curbing the incidence of liver injury triggered by Diethylnitrosamine by declining oxidative stress *via* Nrf2 and NFκB regulation. *Sci Rep* 2018; **8**: 8606 [PMID: 29872102 DOI: 10.1038/s41598-018-26611-1]
- 132 **Domitrović R**, Jakovac H, Romić Z, Rahelić D, Tadić Z. Antifibrotic activity of Taraxacum officinale root in carbon tetrachloride-induced liver damage in mice. *J Ethnopharmacol* 2010; **130**: 569-577 [PMID: 20561925 DOI: 10.1016/j.jep.2010.05.046]
- 133 **Sen A**, Ozkan S, Recebova K, Cevik O, Ercan F, Kervancioglu Demirci E, Bitis L, Sener G. Effects of Myrtus communis extract treatment in bile duct ligated rats. *J Surg Res* 2016; **205**: 359-367 [PMID: 27664884 DOI: 10.1016/j.jss.2016.06.094]
- 134 **Kim HG**, Han JM, Lee HW, Lee JS, Son SW, Choi MK, Lee DS, Wang JH, Son CG. CGX, a multiple herbal drug, improves cholestatic liver fibrosis in a bile duct ligation-induced rat model. *J Ethnopharmacol* 2013; **145**: 653-662 [PMID: 23228913 DOI: 10.1016/j.jep.2012.12.005]
- 135 **Cai Q**, Wang Z, Zhang R, Zhang L, Cui S, Lin H, Tang X, Yang D, Lin X, Bai S, Gao J, Yang L. Huangjia Ruangan Granule Inhibits Inflammation in a Rat Model with Liver Fibrosis by Regulating TNF/MAPK and NF-κB Signaling Pathways. *Evid Based Complement Alternat Med* 2022; **2022**: 8105306 [PMID: 35942372 DOI: 10.1155/2022/8105306]



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