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REVIEW

Traditional Medicine Research 2022;7(6):58. https://doi.org/10.53388/TMR20220219002

Oriental Medicine

Advances in traditional Chinese medicine for liver disease therapy in 2021

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Author contributions

Wei-Bo Wen and Shu-Quan Lyu conceived of the presented idea. Jun-Yu Luo and Jia-Bao Liao contributed to the manuscript preparation and modification with support from Jun-Yu Luo. Jun-Yu Luo contributed to the hepatitis, liver injury, metabolic associated fatty liver disease, cholestasis as well as conclusion and perspective in the manuscript. Jia-Bao Liao contributed to the abstract, liver fibrosis, hepatocellular carcinoma and other liver diseases in the manuscript. Yu-Ming Wang, Jie Zhao, Xue-Hua Xie, Fei Qu, Xi-Xing Fang were responsible for searching and screening all the literature. All authors provided critical feedback and helped revise the final manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by the First Clinical Medical School Project of Yunnan University of Traditional Chinese Medicine (No. 2021Y10), the Bio-Pharmaceutical Major Science and Technology Special Project of Science and Technology Department of Yunnan Province (No. 2019ZF005), the National Natural Science Foundation of China, Youth Science Foundation Project (No. 82104802), the Department of Science and Technology of Yunnan Province, General Project of TCM Joint Special Project (No. 202101AZ070001-064), the Jiaxing Science and Technology Bureau, Applied Basic Research (No. 2022AY10003), the Cangzhou Science and Technology Bureau project (No. 213106042), and the Department of Science and Technology of Yunnan Province, General Project of TCM Joint Special Project (No. 202001AZ070001-058). We thank Editage Ltd. for editing the English text of a draft of this manuscript.

Abbreviations

ALI, acute liver injury; MAFLD, metabolic-associated fatty liver disease; LF, liver fibrosis; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; CLD, cholestatic liver diseases; TCM, traditional Chinese medicine; CFDA, China Food and Durg Adminnistration; STAT3, signal transducer and activator of transcription 3; HBV, hepatitis B virus; TGF-β, transforming growth factor-beta; CCNB1, cyclin B1; JAK2, Janus kinase 2; TNF-α, tumor necrosis factor-alpha; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IL, interleukin; ROS, reactive oxygen species; HO-1, heme oxygenase-1; SOD, superoxide dismutase; GSH, glutathione; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; TG, triglyceride; FXR, farnesoid X receptor; SIRT1, sirtuin 1; HSC, hepatic stellate cells; NF-κB, nuclear factor kappa-B.

Peer review information

Traditional Medicine Research thanks Jian-Wei Jia and other anonymous reviewers for their contribution to the peer review of this paper.

Citation

Luo JY, Liao JB, Wang YM, et al. Advances in traditional Chinese medicine for liver disease therapy in 2021. *Tradit Med Res*. 2022;7(6):58. doi: 10.53388/TMR20220219002.

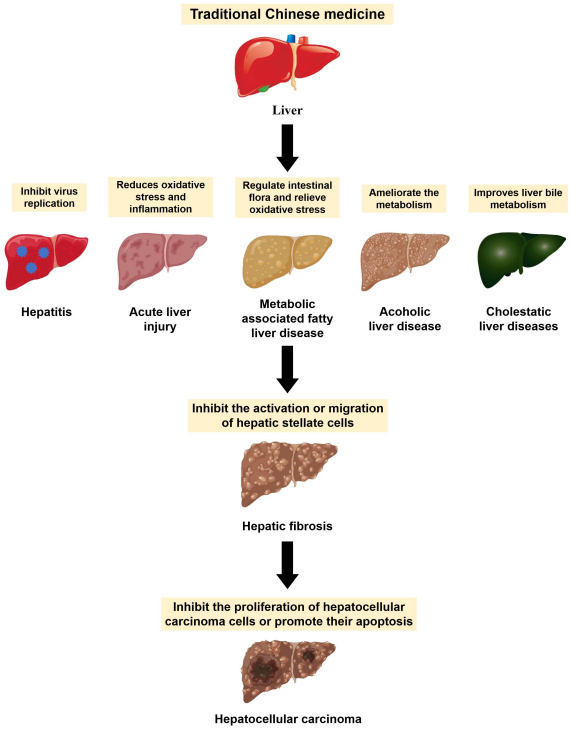
Executive editor: Shan-Shan Lin.

Received: 19 February 2022; **Accepted:** 05 April 2022; **Available online:** 23 May 2022.

Abstract

Liver diseases and their co-morbidities represent a major public health problem. Owing to its progressive pathogenesis and lack of effective treatment, liver disease has become one of the most important causes of death worldwide. Traditional Chinese medicine (TCM) has potential advantages in the prevention and treatment of liver diseases, including high safety, remarkable curative effects, and low toxicity and side effects. In 2021, TCM extracts and their derivatives, TCM compounds, and ethnic medicines showed good efficacy in the treatment of liver diseases. The main mechanisms and representative drugs of TCM can be summarized by the use of amygdalin, dicoumarol, quercetin, and ancient ephedrine decoction to treat hepatitis by inhibiting viral replication, as well as the use of *Gentianae Radix*, lupeol, *Zornia diphylla* (L.) Pers., and Chinese patent medicine Liuwei Wuling tablet to alleviate acute liver injury by improving oxidative stress and inflammatory responses in the body. In the treatment of alcoholic liver disease and metabolic-associated fatty liver disease, the mechanism of TCM is the inhibition of oxidative stress, improving metabolism, regulating intestinal microflora, and enhancing intestinal barrier function. The representative TCM for alcoholic liver disease includes astragaloside, puerarin, patchouli alcohol, and *Mori Fructus* polysaccharide, while those for metabolic-associated fatty liver disease include saikosaponin, dehydroabietic acid, hesperetin, berberine, and *Panax Notoginseng* saponins. Additionally, germacrone, forsythin, geniposide, and protocatechuic acid can inhibit the activation or migration of stellate cells and improve liver fibrosis. Toosendanin, paeoniflorin, chrysin, and the classical prescription Huanglian decoction can significantly inhibit the proliferation of liver cancer cells and promote their apoptosis for the treatment of hepatocellular carcinoma. The activation of the farnesol X receptor pathway can improve bile metabolism in the liver, thus, significantly alleviating cholestatic liver disease. Its representative drugs include the TCM extracts pterostilbene and arbutin. In this review, we summarize the advances made in research on TCM used in the treatment of liver diseases in 2021, providing a reference for further development of TCM for the prevention and treatment of liver diseases.

Keywords: liver disease; traditional Chinese medicine; extracts; therapeutic mechanism; intestinal barrier; intestinal flora



Traditional Medicine Research 2022;7(6):58. https://doi.org/10.53388/TMR20220219002

Highlights

This review summarizes the advances made in research on traditional Chinese medicine for the treatment of liver diseases in 2021. Chinese herbal extracts and their derivatives, Chinese herbal prescriptions, and ethnic medicines have shown good efficacy in the treatment of liver disease. Due to the newfound importance of the gut-liver axis, increasing attention has been paid to the mechanism of repair and restoration of intestinal barrier function and the regulation of intestinal flora in the treatment of liver diseases.

Background

The recent years has witnessed an increase in the number of patients with liver disease worldwide, which is gradually developing into a global risk to public health. Liver diseases include viral hepatitis, acute liver injury (ALI), metabolic-associated fatty liver disease (MAFLD), liver fibrosis (LF), alcoholic liver disease (ALD), hepatocellular carcinoma (HCC), and cholestatic liver diseases (CLD). According to epidemiological statistics, 2 million people die each year from end-stage liver diseases, such as viral hepatitis, cirrhosis, and HCC [1]. However, the clinical use of Western medicine in the treatment of liver diseases is still in its infancy, and is currently characterized by poor efficacy, side effects, high prices, and high drug resistance. As a safe and effective candidate treatment, traditional Chinese medicine (TCM) presents several advantages, including its multi-component, multi-channel, and multi-target properties. Thus, TCM has good potential and broad prospects for the prevention and treatment of liver diseases.

In contrast to 2020, research on liver diseases in 2021 has been more inclined towards the exploration of the mechanisms underlying the action of TCM in the treatment of liver diseases through in vitro and in vivo experiments using modern biotechnologies, such as network pharmacology, western blot analysis, metabolomics research, and 16S rRNA sequencing. In particular, the use of monomers and their derivatives have received increasing attention from researchers. For example, trilobolide-6-O-isobutyrate, isolated from *Trifolium* spp., has been used to induce apoptosis and inhibit the activation of signal transducer and activator of transcription 3 (STAT3) pathway to effectively cease tumor growth. Similarly, dicoumarol, derived from *Medicago sativa* L., inhibits hepatitis B virus (HBV) replication. Moreover, research on the mechanism of action of *Astragali Radix* (widely used in TCM) in the treatment of liver diseases has increased in the past year. Astragaloside, Huangqi decoction, and prescriptions composed of *Astragali Radix* have been found to have remarkable curative effects in the treatment of ALD, MAFLD, LF, CLD, and other common liver diseases. This review systematically summarizes the status of *Astragali Radix* research in the treatment of liver diseases (Table 1) [2–9]. TCM research has focused on several drugs. The TCM *Catechu* has often been used to treat trauma. Its extract, protocatechuic acid, plays a therapeutic role by regulating the transforming growth factor-beta (TGF-β) signaling pathway and downregulating the expression of hepatic fibrosis-related proteins. Gegen Qinlian decoction is used to treat gastrointestinal damp-heat diseases. Additionally, it improved liver steatosis and injury in MAFLD, and its mechanisms may involve regulating inflammatory cytokines and anti-oxidative stress, as well as inhibiting the activation of the NLRP3 signaling axis. In addition, as an important component of TCM, ethnic medicine has a good curative effect in the treatment of liver diseases. For example, the Tujia liver-protecting drug, *Spatholobi Caulis* extract (*Kadsura heteroclita*), effectively relieved liver damage by inhibiting oxidative stress.

Enterohepatic circulation refers to the bidirectional relationship between the gut, its microbes and the liver through the portal vein, biliary tract, and bile secretion system [10]. Many studies have confirmed that alterations in the gut microbiota underlie disorders of the gut-liver axis in patients with liver disease, and are associated with the disease severity and prognosis. This is attributed to the overgrowth and imbalance of the intestinal flora, which damages the natural intestinal barrier. This results in the overgrowth of bacteria and increased secretion of their metabolites, which reach the liver through the portal vein, triggering endotoxemia in hepatic Kupffer cells. Inflammatory responses cause fibrotic responses in hepatic stellate cells (HSC) and consequently stimulate the immune cells, increasing barrier dysfunction and leading to further development of liver disease [11]. Microbially-derived metabolites, including trimethylamine, secondary bile acids, and short-chain fatty acids, are closely related to the development of MAFLD [12]. Alcohol disrupts the relative abundance of the intestinal microbiome, mucus barrier, epithelial barrier, and antimicrobial peptide production levels, which increases microbial exposure and the pro-inflammatory environment in the liver, leading to ALD [13]. Liver cirrhosis is associated with live bacterial translocation, bacterial infection, and a severe disturbance of the gut barrier [14]. Therefore, using TCM to target the regulation of intestinal microecological balance to prevent bacterial translocation and inflammatory response has potential for the prevention and treatment of liver diseases. Sea buckthorn (*Hippophae Fructus*) fermentation liquid has been previously found to increase the ratio of *Firmicutes/Bacteroidetes* in the intestinal flora, consequently increasing the abundance of beneficial bacteria, such as *Lactobacillus*, and thereby ameliorating alcoholic liver injury in mice [15]. Zhuyu pill, a classic ancient TCM prescription, is used to treat CLD by restoring the imbalance of intestinal flora, increasing beneficial bacteria (*Bacteroidetes*, *Lactobacillus*, and *Actinobacteria*) and pathogenic bacteria (*Gammaproteobacteria*), and exerting an anti-cholestatic effect [16–17]. A summary of the application of therapeutic mechanisms related to intestinal barrier function and intestinal flora in liver diseases in 2021 is provided in Table 2 [15–27].

To elucidate the detailed mechanisms underlying the action of TCM in the treatment of liver disease, studies have not only verified the efficacy of TCM using in vivo models, but have also established in vitro models combined with in vitro and in vivo experiments. Therefore, the development of advanced, safe, and effective in vitro models is imperative. Studies in 2021 have highlighted several advantages of liver passaged cell lines, including high replication ability, good stability, easy handling, and long lifespan. Thus, these cells have been often used for the establishment of in vitro models. For example, HepG2 cells, L02 cells, and HuH7 cells are commonly used for MAFLD lipid metabolism, while HepaRG cells are recommended for drug metabolism and toxicity studies [28]. In addition, three-dimensional cell culture models, such as liver spheroids, liver organoids, and liver chips, are being increasingly used in studies. These models help researchers select appropriate cells and culture conditions according to the research objectives and obtain high-quality results. In addition, numerous new techniques in liver disease research have been developed, including proteomics, RNAi, gene knockout, single-cell RNA sequencing, and transcriptome sequencing technology [29]. A study on used the classic prescription Huanglian decoction in the cyclin B1(CCNB1) gene knockout model in vitro and confirmed that Huanglian decoction can significantly inhibit the growth, migration, and invasion of HCC cells [30].

A PubMed database search has revealed that, in 2021, research on TCM comprised numerous experimental and clinical studies on the efficacy and mechanism of single TCM extracts and TCM compound prescriptions in the treatment of liver diseases. Therefore, significant advances have been made in the treatment of several different liver diseases, as summarized in the following sections.

Hepatitis

Hepatitis includes hepatitis A, B, C, and E, among which hepatitis B has the highest incidence rate. According to the Chinese Center for Disease Control and Prevention, approximately 90 million HBV

Table 1 Characteristics of the included studies relevant to the mechanisms of action of *Astragali Radix* in treatment of liver disease

Disease	Type	Extract/ formula	Sample	Inteventions	Primary results	Reference
ALD	In vitro & vivo	Astragaloside	A rat model of ALD and the hepatocyte cell line AML-12.	Astragaloside was administered to rats orally at 25 mg/kg every day. And for ethanol and astragaloside treatment, AML-12 cells were treated with ethanol at 50, 75, 100, 150 or 200 mM in combination with astragaloside at 50, 75, 100, 150 or 200 μg/mL for 48 h.	Astragaloside reduced lipid accumulation and inflammation in the liver, suppressed hepatocyte apoptosis and improved liver function in rat models. Mechanistically, astragaloside inhibited alcohol-induced ROS generation and oxidative stress in the liver to exert its functions.	[2]
MAFLD	In vitro	Qihu preparation	Thirty-seven BKS-Leprem2Cd479 /Nju (db/db) and eight C57BLKS/JNju (BKS) mice.	Qihu group (0.75 g/kg, 1.5 g/kg, 3 g/kg). The drugs were administered twice a day at an interval of more than 4 h for 28 days.	Qihu preparation significantly downregulated and the swelling and steatosis of the hepatocytes were significantly lower. Qihu downregulated the expression of IL-1 beta, IL-6, and thioredoxin interacting protein and upregulated the AMP-activated protein kinase signaling pathway in the pancreas and liver tissues of db/db mice.	[3]
MAFLD	In vitro	Qinghua formula	High-fat diet (88% regular Yfeed, 10% lard, and 2% cholesterol) induced sixty male Wistar rats.	Qinghua formula was administered to the rats at 1 mL/100 g (equivalent to the human dose). Three of the high-fat diet groups were given Qinghua formula by oral gavage at three dose levels: high, middle and low levels (0.8, 0.4, and 0.2 g/100 g body weight, respectively).	Qinghua formula alleviated the liver dysfunction and increased blood lipid levels of MAFLD rats induced by high-fat diet. It also effectively reduced the degree of liver steatosis and adjusted the number and structure of intestinal flora. Treatment with Qinghua formula had a significant effect on MAFLD.	[4]
LF	In vitro	*Astragali Radix*	36 CCl_4-induced Sprague-Dawley rats.	Eight weeks later, the *Astragali Radix* (2.7, 5.4, and 10.8 g/kg/d) groups and colchicine group (0.2 mg/kg/d) were given the corresponding concentration of drugs. The control group and model group were given equal volume of distilled water. All rats were treated by intragastric administration once a day for 6 weeks.	*Astragali Radix* significantly inhibits LF by intervening in the high mobility group box 1-mediated inflammatory signaling pathway and secretion signaling pathway.	[5]
LF	In vitro	Yiqi Huoxue recipe	Wistar rats were used to generate a model of carbon CCl_4-induced LF.	The rats in the Yiqi Huoxue recipe group were treated with Yiqi Huoxue recipe (3.4 g/10 mL/kg body weight) twice weekly via gavage for eight weeks.	In conclusion, the findings have demonstrated that Yiqi Huoxue recipe treatment attenuates LF in rats. Furthermore, these data suggest that Yiqi Huoxue recipe may exert its anti-fibrotic activity through inhibiting Yes-associated protein/transcriptional coactivator with PDZ-binding motif signaling. As such, the findings may contribute to a better understanding of the mechanisms by which Yiqi Huoxue recipe exerts an anti-fibrotic effect during the treatment of LF.	[6]

Table 1 Characteristics of the included studies relevant to the mechanisms of action of *Astragali Radix* in treatment of liver disease (*continued*)

Disease	Type	Extract/ formula	Sample	Inteventions	Primary results	Reference
LF	In vitro	Baoganning formula	25% CCl_4 (in olive oil)-induced C57BL/6 mice.	Baoganning formula low, medium and high concentration groups were given 0.88, 1.76 and 3.51 g/mL, respectively, for 8 weeks.	Baoganning formula can effectively inhibit LF in mice possibly by lowering the expression level of indoleamine 2,3dioxygenase 1 in the liver, thus improving the function of hepatic dendritic cells and subsequently promoting proliferation of T cells.	[7]
HCC	Meta-analysis	Kang-ai injection	Data pertaining to 35 trials with 2,501 HCC patients were analysed.	The Web of Science, PubMed, Cochrane Library, Embase, China Biology Medicine database, China National Knowledge Infrastructure, VIP database and Wanfang database were systematically searched (date range: inception to December 2020) using the key terms “Kang-ai injection” and “hepatocellular carcinoma”. The current analysis included controlled clinical trials that compared the efficacy and safety of the combination of Kang-ai injection and conventional treatment with conventional treatment alone for HCC. The current study estimated the pooled risk ratio with 95% confidence intervals.	The current meta-analysis indicates that a combination of conventional treatment and Kang-ai injection could be more effective in improving the clinical efficacy of the treatment of HCC, compared to conventional treatment alone.	[8]
CLD	In vitro	Huangqi decoction/ astragalosides	ANIT olive oil solution (2%) induced six weeks old male Wistar rats.	ANIT group, received the ANIT solution continuously till 12 weeks; HQD treated group, oral garage ANIT as processed in ANIT group and received a daily dose of 720 mg/kg of body weight HQD once a day for 4 consecutive weeks from week 9 to week 12; astragalosides group, oral garage ANIT as processed in ANIT group and received a daily dose of 125 mg/kg of body weight astragalosides once a day for 4 consecutive weeks from week 9 to week 12.	Intervention by ANIT can significantly change the homeostasis of bile acids and free fatty acids. Huangqi decoction and astragalosides exerted a hepatoprotective effect against cholestatic liver injury by restoring the altered bile acid and free fatty acid metabolism through the improvement of bile acid transporter, nucleus hormone receptor, and membrane receptor.	[9]

Qihu preparation: empirical formula, composition by *Panax Notoginseng*, *Lonicerae Japonicae Flos*, *Dendrobii Caulis*, *Puerariae Thomsonii Radix*, *Astragali Radix*. Qinghua formula: empirical formula, composition by *Astragali Radix*, *Atractylodis Rhizoma*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*, *Panax Ginseng*, *Glycyrrhizae Radix*, *Angelicae Sinensis Radix*, *Smilacis Glabrae Rhizoma*. Yiqi Huoxue recipe: empirical formula, composition by *Astragali Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Curcumae Longae Rhizoma*, *Smilacis Glabrae Rhizoma*, *Amomum kravanh Pierre* ex *Gagneop*. Baoganning formula: empirical formula, composition by turtle shell, *Whitebackleaf Mallotus* Root, *Astragali Radix*, *Scutellariae Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*. Kang-ai injection: Chinese patent medicine (China Food and Durg Adminnistration approval number: Z20026868), composition by *Panax Ginseng*, *Astragali Radix*, *Sophorae Flavescentis Radix*. Huangqi decoction: classical formula, composition by *Astragali Radix*, *Sesamum Indicum*, white honey, *Citri Reticulatae Pericarpium*. ALD, alcoholic liver disease; MAFLD, metabolic-associated fatty liver disease; LF, liver fibrosis; CCl_4, tetrachloride; IL, interleukin; ROS, reactive oxygen species; HCC, hepatocellular carcinoma; CLD, cholestatic liver diseases; ANIT, α-naphthylisothiocyanate.

Table 2 Treatment of liver disease by regulating intestinal flora and restoring intestinal barrier function

Disease	Extrat/ formula	Origin/ composition	Part	Type	Inteventions	Primary results	Reference
ALD	Sea buckthorn fermentation liquid	*Hippophae Fructus*	Fruit	In vivo	Sea buckthorn fermentation liquid was used to construct alcoholic liver injury mouse model, and the experimental group was treated with sea buckthorn fermentation liquid (1.75, 2.68, 5.35 g/kg) intragastally for 15 days.	Sea buckthorn fermentation liquid protected against ALD and modulated the composition of gut microbiota.	[15]
	Patchouli alcohol	*Pogostemonis Herba*	Herb	In vivo	Male Wistar rats orally received patchouli alcohol (10, 20, or 40 mg/kg) and silymarin (200 mg/kg) for ten days. On the 8th day, the rats orally received 65% ethanol (10 mL/kg, 6.5 g/kg) every 12 h for 3 days.	Patchouli alcohol ameliorates ethanol-induced ALD via restoration of CYP2E1/ROS/nuclear factor erythroid 2/HO-1-mediated oxidative stress and AMP-activated protein kinase-mediated fat accumulation, as well as alleviation of gut-lipopolysaccharide -leakage-induced inflammation regulated by the MyD88/TLR4/NF-κB signaling pathway.	[18]
MAFLD	*Panax Ginseng* saponins	*Panax Ginseng*	Root	In vivo	Male C57BL/6J mice at 6 weeks old were fed a HFD (60% fat, research diets, D12492) throughout the 12-week experimental period. The leptin ob/ob and HFD mice were fed their respective diets for 4 weeks to induce obesity related NAFLD before oral administration of *Panax Ginseng* saponins (800 mg/kg per day) for an additional 8 weeks. The HFD and ob/ob mice were euthanized for the collection of serum, liver and small intestine tissues.	*Panax Ginseng* saponins exerted hepatoprotection against NAFLD in both ob/ob and HFD-induced obese mice, primarily by mediating the gut-liver axis in a TLR4-dependent manner.	[19]
	Ginsenosides	*Panax Ginseng*	Root and rhizome	In vivo	Six-week-old C57BL/6J male mice were raised under specific pathogen free conditions and had free access to their diet and water. After an adaptive period of 1 week, the mice were randomly divided into four groups: 1) the normol diet group was administered a normal chow diet (10% calories from fat); 2) the HFD group was administered a HFD (60% calories from fat); 3) the ginsenosides low group was administered the HFD supplemented with 100 mg ginsenosides/kg body weight; 4) the ginsenosides high group was administered the HFD supplemented with 200 mg ginsenosides/kg body weight. The experiment lasted for a total of 12 weeks.	Ginsenosides ameliorated HFD-induced MAFLD by maintaining the energy balance, modulating gut dysbiosis, and improving the intestinal integrity and metabolic inflammation.	[20]

Table 2 Treatment of liver disease by regulating intestinal flora and restoring intestinal barrier function (*continued*)

Disease	Extrat/ formula	Origin/ composition	Part	Type	Inteventions	Primary results	Reference
MAFLD	Qinghua formula (empirical formula)	*Astragali Radix*, *Atractylodis Rhizoma*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*, *Panax Ginseng*, *Glycyrrhizae Radix*, *Angelicae Sinensis Radix*, *Smilacis Glabrae Rhizoma*	–	In vivo	Qinghua formula was administered to rats at 1 mL/100 g (equivalent to the human dose). Three of the HFD groups were given Qinghua formula by oral gavage at three dose levels: high, middle and low levels (0.8, 0.4, and 0.2 g/100 g body weight, respectively).	Qinghua formula alleviated the liver dysfunction and increased blood lipid levels of MAFLD rats induced by HFD. It also effectively reduced the degree of liver steatosis and adjusted the number and structure of intestinal flora. Treatment with Qinghua formula had a significant effect on MAFLD.	[4]
	919 syrup (patent number: CN107929413B)	Kiwifruit, *Sophorae Flavescentis Radix*, *Atractylodis Rhizoma*, *Sophorae Flavescentis Radix*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*	–	In vivo	Twenty male Sprague-Dawley rats were randomly divided into the control and 919 syrup groups (n = 10 per group). Both groups received a standard diet each day, and while rats in the 919 syrup group were fed 919 syrup daily, rats in the control group were given the same volume of saline daily for 4 weeks.	919 syrup may have therapeutic effects on MAFLD by regulating feed intake, body weight and the balance of intestinal microbiota, and is a promising therapeutic drug for treatment of MAFLD.	[21]
	Si Miao formula (classic formula)	*Atractylodis Rhizoma*, *Phellodendri Chinensis Cortex*, *Achyranthis Bidentatae Radix*, *Coicis Semen*	–	In vivo	The mice in the intervention group were treated with low-dose Si Miao formula (10 g/kg) and high-dose Si Miao formula (20 g/kg), respectively by intragastric administration once a day for 16 weeks.	The results indicate that Si Miao formula attenuates NAFLD and regulates hepatic lipid metabolism pathways. The anti-NAFLD effect of Si Miao formula was linked to modulation of the gut microbiota composition and in particular an increased relative abundance of *Akkermansia muciniphil*a.	[22]
LF	Phillygenin	*Forsythiae Fructus*	Dried fruit	In vivo	Except for the normal control group and the solvent control group, mice in the other groups were injected with CCl_4 dissolved in olive oil (1:9, v/v) three times a week (2 mL/kg) intraperitoneally for 4 weeks to establish LF model. The solvent control mice were injected with olive oil alone at the same volume and frequency. Phillygenin was dissolved in a 0.5% sodium carboxymethyl cellulose solution. Mice were given phillygenin (intragastric administration) every day for 4 weeks.	Phillygenin restored the intestinal epithelial barrier by promoting the expression of intestinal barrier markers, including zonula occludens-1, occludin and Claudin-1. Phillygenin treatment enriches the relative abundance of *Lactobacillus*, which is reported to alleviate inflammation and fibrosis of damaged liver. Collectively, phillygenin attenuates CCl_4-induced LF partly via modulating inflammation and gut microbiota.	[23]

Table 2 Treatment of liver disease by regulating intestinal flora and restoring intestinal barrier function (*continued*)

Disease	Extrat/ formula	Origin/ composition	Part	Type	Inteventions	Primary results	Reference
	Evodiamine	*Euodiae Fructus*	Fruit	In vivo	Mice in control group received intraperitoneal injection of olive oil (2 mL/kg, twice per week) for 6 weeks. Mice in model and evodiamine groups received intraperitoneal injection of 20% CCl_4 (2 mL/kg, twice per week) for 6 weeks to induce LF mice. Then, mice in evodiamine group received orally of evodiamine (18 mg/kg) for 4 weeks.	Evodiamine can ameliorate CCl_4-induced LF through modulating gut microbiota and inhibiting the inflammatory response in liver.	[24]
	CGEA	*Cichorium Pumilum* Jacq	Root	In vivo	Twice a week for 12 weeks, starting at week 13, except for the blank control group, the rats were randomly divided into model group, positive group, high dose group of CGEA (CGEA-150 mg kg 1), low dose group of CGEA (CGEA-100 mg/kg)	The prevention of LF caused by intestinal inflammation by CGEA may be achieved by regulating the intestinal microbiota and restoring the intestinal barrier thereby improving the “gut-liver axis” circulation, reducing liver inflammation, and ultimately alleviating LF.	[25]
	Ganshuang granules (Chinese patent medicine, Z20027671)	*Bupleuri Radix*, *Paeoniae Alba Radix*, *Angelicae Sinensis Radix*, *Smilacis Glabrae Rhizoma*, *Atractylodis Macrocephal* ae *Rhizoma*	–	In vivo	CCl_4-induced hepatic fibrosis models were allocated into 4 groups receiving normal saline (model), 1, 2, or 4 g/kg Ganshuang granules for 5 weeks.	Ganshuang granules decreased the intestinal permeability and rebalanced the gut microbiota to reduce the oxidative stress and inflammation, eventually attenuating CCl_4-induced hepatic fibrosis.	[26]
CLD	ZYP (classic formula)	*Coptidis Rhizoma*, *Euodiae Fructus*	–	In vivo	ZYP was given to the treatment groups at doses of 0.6 (ZYP), 1.2 (ZYP) g/kg body weight, respectively, six times before and four times after they were treated with 50 mg/kg α-naphthyl isothiocyanate by gavage. In this study, ZYP doses that were adopted were based on the maximum recommended clinical dose (12 g/60 kg/day).	α-Naphthyl-isothiocyanate altering of blood biochemical and metabolic profiles and of fecal microbiota could effectively be alleviated with ZYP treatment.	[27]

ALD, alcoholic liver disease; MAFLD, metabolic-associated fatty liver disease; ROS, reactive oxygen species; HO-1, heme oxygenase-1; HFD, high-fat diet; LF, liver fibrosis; CLD, cholestatic liver diseases; NAFLD, non-alcoholic fatty liver disease; CCl_4, tetrachloride; CGEA, *Cichorium pumilum* Jacq ethyl acetate extract; ZYP, Zhuyu pill; –, not mentioned.

carriers currently reside in China, which ranks first in the world in terms of the number of affected individuals [31]. This has given rise to an urgent need to develop efficient, drug-resistant, and specific hepatitis B treatment drugs to relieve pressure on both doctors and their patients. Although Western medicine has made significant progress in the diagnosis and treatment of this disease in recent years, significant shortcomings continue to persist, including side effects and high costs, which restrict its application and efficacy. TCM has been used since thousands of years in the treatment of liver disease, and an increasing number of studies have shown that TCM represents a good strategy for the inhibition of virus replication, as well as alleviating liver damage (Table 3) [32–37].

Table 3 The representative traditional Chinese medicine for treating hepatitis B

Extrat/ formula	Origin/ composition	Part	Type	Interventions	Primary results	Reference
Amygdalin	*Armeniacae Semen Amarum*	Fruit	In vitro	HepG2.2.15 cells and T cells co-culture. T-cells were treated with 5, 10, 15 or 20 μg/mL amygdalin for 24, 48 and 72 h, and collected for further experiments.	These findings all indicate that amygdalin treatment could increase the HBV-T cell activity via suppressing the phosphorylation of STAT3 and JAK2, subsequently increases antitumor cytokines production, such as interferon-γ and TNF-α, finally inhibiting the cell growth, invasion, and migration while increasing HepG2.2.15 cell apoptosis.	[32]
Dicoumarol	*Medicago sativa* L.	Herb	In vivo & vitro	Author screened 2,000 small-molecule compounds for their ability to inhibit HiBiT-tagged HBx expression by using a HiBiT lytic detection system. The antiviral activity of a candidate compound and underlying mechanism of its effect on covalently closed-circular DNA transcription were evaluated in HBV-infected cells and a humanised liver mouse model.	Author identified that the small molecule dicoumarol could block covalently closed-circular DNA transcription by promoting HBx degradation; this is a promising therapeutic strategy for the treatment of chronic hepatitis B.	[33]
Mahuang decoction	*Ephedra Sinica*, *Armeniacae Semen Amarum*, *Cinnamomi Ramulus*, *Glycyrrhizae Radix*	–	In vitro	A mixture of crude drugs (2-times amount of the daily dose) was boiled with 500 mL of purified water for 17 min, followed by heating for 13 min. The decoction was filtrated and freeze-dried to yield dry extract powder. The extracts were dissolved in ultra-pure water at a concentration of 10 mg/ml. HepG2 HepAD38.7 and HepG2-NTCP cell models were established in vitro.	Mahuang decoction suppressed HBV production by interfering with HBV nucleocapsid incorporation into virions, possibly through reduction of the expression of tropomyosin 2 beta.	[34]
LCF (empirical formula)	*Bupleuri Radix*, *Solanum nigrum* L, *Hedyotis diffusa* Willd, *Ligustri Lucidi Fructus*, *Gardeniae Fructus*, *Glycyrrhizae Radix*	–	In vivo	(I) a model group; (II) a positive control-LAM group (0.2 g/kg); (III) a low-dose LCF (2 g/kg) group; (IV) a medium-dose LCF (15 g/kg) group; and (V) and a high-dose LCF (45 g/kg) group. Intragastric administration once a day for 10 days.	LCF significantly inhibited DHBV-deoxyribonucleic acid replication on day 10 and day 3 after the cessation of treatment. Notably, the low-dose LCF group showed the best inhibitory effect. The obviously sustained anti-DHBV activity of LCF inhibited viral replication, and a rebound reaction was found. Phosphatidylcholine and phosphatidylethanolamine classes, which are mainly involved in liver cell repair and energy metabolism through phospholipid metabolic pathways, were identified by metabolomics analysis.	[35]

Table 3 The representative traditional Chinese medicine for treating hepatitis B (*continued*)

Extrat/ formula	Origin/ composition	Part	Type	Interventions	Primary results	Reference
LWWL (Chinese patent medicine, Z20060238)	*Schisandrae Chinensis Fructus*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Sophorae Flavescentis Radix*, *Tsaoko Fructus*, *Scutellariae Radix*	–	In vivo & In vitro	The cells in duplicate wells were treated with different concentrations of the drug (0, 0.1, 0.2, 0.4 and 0.8 mg/mL of LWWL, or 0, 0.2, 2, 20, 200 μmol/L of tenofovir disoproxil fumarate, or selective concentrations of compounds identified from LWWL) for 5 days. Normal saline group, low-dose LWWL (1 g kg/d) group, high-dose LWWL (2 g kg/d) group, and tenofovir disoproxil fumarate (63 mg kg/d) group. Intraperitoneal injection was conducted once a day for 4 weeks.	LWWL had potent inhibitory effect on both wild-type and entecavir-resistant HBV, which might be associated with increasing interferon-beta and interferon-gamma production.	[36]
EZJDR (empirical formula)	*Atractylodis Macrocephalae Rhizoma*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Hedyotis diffusa* Willd, turtle shell	–	Clinical trials	A total of 72 patients of Hepatitis B Cirrhosis with hyperalphafetoproteinemia were randomized in 2 parallel groups. Patients in the control group received placebo granules similar to the EZJDR. In the EZJDR group, patients received EZJDR twice a day, after meals, for 48 weeks.	The results showed that EZJDR can significantly inhibit the levels of alpha-fetoprotein and alpha-fetoprotein L3 in patients with hepatitis B cirrhosis and hyperalphafetoproteinemia and have good security.	[37]

HBV, hepatitis B virus; STAT3, signal transducer and activator of transcription 3; JAK2, Janus kinase 2; TNF-α, tumor necrosis factor-alpha; LCF, Long Chai formula; LWWL, Liuwei Wuling tablet; EZJDR, Erzhu Jiedu recipe; –, not mentioned.

In a study published in 2021, Wang et al. co-cultured HepG2.2.15 cells with T cells to establish an in vitro HBV T cell model and found that amygdalin extracted from *Armeniacae Semen Amarum* inhibited the phosphorylation of STAT3 and Janus kinase 2 (JAK2) by inhibiting the activity of HBV-T cells and increasing the production of anti-tumor cytokines, such as interferon-γ and tumor necrosis factor-alpha (TNF-α). This suggests that amygdalin suppresses HBV infection through T cell-mediated tumor immunity [32]. NAD(P)H:quinone oxidoreductase 1 binds and protects HBx (a type of HBV genome) protein from 20S proteasome-mediated degradation. The TCM dicoumarol, a derivative of the TCM *Medicago sativa* L., significantly reduced HBx expression through covalently closed-circular DNA and inhibited covalently closed-circular DNA transcription by inhibiting NAD(P)H:quinone oxidoreductase 1, thereby inhibiting HBV replication [33]. Based on network pharmacology analysis, the active ingredient of *Artemisiae Annuae Herba* quercetin was found to exert therapeutic effects by acting on several targets, including protein kinase B and interleukin (IL)-8, via key signaling pathways, namely Toll-like receptors, hepatitis B, cellular senescence, and chemokines [38]. A meta-analysis showed that the clinical treatment of HBV with kushenin, the main component of *Sophorae Flavescentis Radix*, combined with adefovir dipivoxil or entecavir significantly reduced serum HBV DNA and HBeAg levels and improved clinical efficacy compared with that of Western medicine [39]. By establishing HepG2, HepAD38.7, and HepG2-NTCP cell models in vitro, researchers found that the TCM Mahuang decoction (composed of *Ephedra Sinica*, *Armeniacae Semen Amarum*, *Cinnamomi Ramulus and Glycyrrhizae Radix*) interfered with HBV nucleocapsid binding to virions, while at the same time reducing the host gene tropomyoglobin. In another study, the expression of tropomyosin 2 beta protein was found to inhibit HBV replication [34]. Professor Shi Jin's own Long Chai formula (composed of *Bupleuri Radix*, *Solanum nigrum* L, *Hedyotis diffusa* Willd, *Ligustri Lucidi Fructus*, *Gardeniae Fructus and Glycyrrhizae Radix*) was administered intragastrically to a HBV-DNA duck model, and significantly reduced HBV-DNA. After three days of drug withdrawal, HBV replication showed no apparent rebound. Metabolomic analysis showed that Long Chai formula may repair liver cell damage via phospholipid metabolism [35]. The Liuwei Wuling tablet (China Food and Durg Adminnistration (CFDA) approval number: Z20060238; composed of *Schisandrae Chinensis Fructus*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Sophorae Flavescentis Radix*, *Tsaoko Fructus and Scutellariae Radix*) is a Chinese patent medicine approved for the treatment of chronic HBV infection and inflammation. Its mechanism of action involves the inhibition of HBV replication by increasing interferon-beta and interferon-g activity [36]. In a 48-week randomized, double-blinded, placebo-controlled clinical trial including 72 patients with hepatitis B, the self-drawn prescription of Erzhu Jiedu decoction (composed of *Atractylodis Macrocephalae Rhizoma*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Hedyotis diffusa* Willd and turtle shell) was found to significantly inhibit the levels of alpha-fetoprotein and alpha-fetoprotein L3 in the patients [37].

ALI

ALI refers to sudden liver cell damage occurring over a short period of time, often related to drug poisoning, viral infection, immune response, and ischemia-reperfusion. If ALI is not treated in time, it eventually leads to acute liver failure, posing a serious threat to the individual's life. The mechanism of action of TCM in ALI treatment mainly includes improving the state of oxidative stress and inflammatory response in vivo and inhibiting the occurrence of hepatocyte fibrosis and hepatocyte apoptosis. Quercetin, which is extracted from the TCM *Albiziae Cortex*, exerts protective effects on the liver. In vivo studies have shown that quercetin affects the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, IL-6, TNF-α, reactive oxygen species (ROS), superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GSH-Px), catalase, and malondialdehyde (MDA), thereby

effectively attenuating acetaminophen-induced ALI in mice. In vitro studies have also shown that quercetin can maintain the level of mitochondrial complex I and restore its activity in damaged cells, thereby reducing ROS production, protecting the mitochondria from oxidative stress, and exerting protective effects on the liver [40]. *Gentianae Radix* significantly reduced the levels of AST, ALT, TNF-α, monocyte chemoattractant protein-1, IL-6, and MDA, and increased the levels of SOD, GSH, and GSH-Px in rats with ALI. Serum metabolomic analysis showed that *Gentianae Radix* could improve steroid biosynthesis, linoleic acid metabolism, porphyrin and chlorophyll metabolism, and fatty acid biosynthesis [41]. Dandelion could significantly improve liver injury in mice with acetaminophen hepatotoxicity by activating the Nrf-2/heme oxygenase-1 (HO-1) pathway and inhibiting the intrinsic apoptosis pathway; and juice prepared using fresh dandelion was better than that using dried dandelion [42]. Lupeol is a natural triterpenoid widely found in fruits and vegetables, such as olives and green peppers. It has significant antioxidant and anti-inflammatory properties in the treatment of liver diseases. In a mouse model of D-galactosamine/lipopolysaccharide induced ALI, lupeol significantly reduced hepatic inflammatory cell infiltration, decreased pro-inflammatory cytokine levels, and ameliorated oxidative stress. The mechanism underlying the action of this extract may be related to the activation of TGFβ1/nuclear factor erythroid 2 (Nrf2) signaling pathway [43]. *Kadsura heteroclita* is a well-known Tujia liver-protecting drug, also known as *Sargentodoxae Caulis* and has long been used in the prevention and treatment of liver diseases. The ethanolic extract of its rhizomes has been found to significantly improve liver injury induced by carbon tetrachloride (CCl_4) by inhibiting oxidative stress, inflammation, and apoptosis [44]. *Zornia diphylla* (L.) Pers. is a herb that is often used to treat liver diseases. *Zornia diphylla* (L.) Pers. has marked protective and ameliorating effects in CCl_4 induced mouse liver injury model, whose mechanism may involve the inhibition of oxidative stress, reduction in the release of inflammatory factors, and promotion of hepatocyte repair [45]. Liuwei Wuling tablet is a TCM compound used to reduce abnormal transaminase levels caused by various liver diseases. Its main component, luteolin, inhibited H_2O_2 induced apoptosis and the activation of the nuclear factor kappa-B (NF-κB) signaling pathway in macrophages. The main components of schisandrin A and B significantly inhibited the release of ROS in ALI induced by aminophenol, which can play an important role in protecting the liver [46]. In vivo studies on the TCM Xuebijing injection (CFDA approval number: Z20040033; composed of *Carthami Flos*, *Paeoniae Rubra Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Angelicae Sinensis Radix*, and *Chuanxiong Rhizoma*) have shown that it can significantly reduce the liver index (liver weight/body weight) and inhibit the expression of pro-inflammatory factors in the serum. In vitro studies have shown that Xuebijing can significantly alleviate the inflammatory response of lipopolysaccharide-induced RAW264.7 cells in vitro and prevent infectious ALI by regulating the glycogen synthase kinase 3β pathway [47]. In another study, Niujiaodihuang detoxify decoction (composed of buffalo horn, *Paeoniae Rubra Radix*, *Rehmanniae Radix*, *Siphonostegiae Herba*, *Artemisiae Scopariae Herba*, *Moutan Cortex*, *Gardeniae Fructus*, and *Glycyrrhizae Radix*) in D-galactosamine/lipopolysaccharide was used to induced a rat acute liver failure model and an in vitro cell model, in which it reduced the accumulation of labile iron and alleviated the accumulation of lipid peroxidation products by enhancing GSH peroxidase 4 activity. The inhibition of ferroptosis exerts hepatoprotective effects. Further metabolomic analysis showed that this mechanism may be related to the regulation of GSH metabolism [48].

ALD

The clinical incidence of ALD caused by alcohol abuse, alcohol dependence, and alcoholism is increasing every year, becoming a major cause of liver damage, only after viral hepatitis. Jiang et al. established an alcoholic fatty liver disease rat model and an alcoholic fatty liver cell in vitro model using ethanol treatment to evaluate the effects of treatment with astragaloside, the active ingredient of *Astragali Radix*. In vivo studies have shown that astragaloside can inhibit lipid accumulation and oxidative stress and reduce IL-10 expression, while in vitro results showed that astragaloside blocked apoptosis by promoting B-cell lymphoma/leukemia-2 associated protein expression, cytochrome C release, and the inhibition of B-cell lymphoma/leukemia-2 and adenosine-triphosphate expression. Further studies have shown that astragaloside inhibits oxidative stress by blocking the activation of the NF-κB signaling pathway, thereby improving liver function and reducing alcoholic fatty liver disease in rats [2]. *Puerariae Lobatae* radix flavonoids and puerarin are the active components of the TCM *Puerariae Radix*, which regulate alcohol metabolism, lipid metabolism (including CYP2y3, CYP3a65, ADH8a, ADH8b, HMGCRB, and FASN), gene expression related to endoplasmic reticulum stress and DNA damage (CHOP, EDEM1, GADD45αa, and ATF6), and reduce the levels of IL-1β and TNF-α in zebrafish larvae, thereby alleviating alcohol-induced hepatic steatosis. This mechanism is closely related to the regulation of the AMPKα-ACC signaling pathway [49]. *Hippophae Fructus* fermentation liquid significantly improved alcohol-induced liver damage. Analysis if the intestinal flora in mouse fecal samples showed that high-dose *Hippophae Fructus* fermentation liquid significantly increased the ratio of intestinal flora *Firmicutes/Bacteroidetes*, as well as reduced the number of gram-negative *Bacteroidetes*, while significantly reducing the abundance of *Akkermansia*, *Zurich bacillus*, *Alloidobacter*, and *Clostridium rumeni* and increasing the abundance of the beneficial bacteria *Lactobacillus* [15]. Patchouli alcohol, an extract of *Pogostemonis Herba*, significantly reduced histopathological changes in the liver in a model of alcoholic liver injury, reduced the levels of ALT and AST, and enhanced the activities of alcohol dehydrogenase and aldehyde dehydrogenase. In addition, patchouli alcohol significantly inhibited the ROS levels and increased antioxidant enzyme activity via the CYP2E1/ROS/Nrf2/HO-1 signaling pathway, thereby restoring intestinal barrier function, colon histopathology, and changes in richness and evenness of intestinal microbiota induced by acute alcohol [18]. *Mori Fructus* polysaccharide, the main active component of *Mori Fructus*, significantly improved the abnormal concentrations of ALT, AST, triglyceride (TG), SOD, and MDA in the serum. Its mechanism may be related to the regulation of linoleic acid metabolism and alpha linolenic acid metabolism, which are related to various metabolic pathways, such as glycerophospholipid metabolism [50]. Mulberry leaves reversed the acute alcohol-induced liver damage by inhibiting the expression of pro-inflammatory factors and enhancing the activity of antioxidant enzymes. Furthermore, mulberry leaves increased caveolin-1 expression and blocked the EGFR/STAT3/iNOS signaling pathway, thereby reducing hepatocyte apoptosis in a mouse model of alcoholic liver injury [51]. The fermentation liquid of sprouted *Panax Ginseng* is rich in phenolics and flavonoids, has high levels of free radical scavenging activity, can significantly reduce the latency of the righting reflex in ethanol-induced hangover mice, increase the activity and expression of ethanol-metabolizing enzymes, and reduce liver cell necrosis, as well as ALT and AST levels, thereby alleviating ALI caused by hangover and endotoxin [52]. The TCM Wangshi Baochi pills (CFDA approval number: Z2020647; composed of *Coptidis Rhizoma*, *Zingiberis Rhizoma*, *Rhei Radix* et *Rhizoma*, *Fritillariae Cirrhosae Bulbus*, *Arisaematis Rhizoma*, and *Ardisiae Crenatae Radix*) helps to enhance the expression of alcohol dehydrogenase in the liver, shorten the acute alcoholic time required to wake up in liver-injured mice, and protect the liver by reducing serum AST and ALT levels. Wangshi Baochi pills also improve acute alcoholic liver injury in mice by upregulating SOD-1 and NAD(P)H:menadione oxidoreductase 1 expression to inhibit oxidative stress and reduce ROS levels [53].

MAFLD

MAFLD, generally considered a hepatic manifestation of metabolic syndrome, has a global prevalence of 25% and is the leading cause of cirrhosis and HCC. MAFLD ranges from steatosis with or without mild

inflammation to nonalcoholic steatohepatitis. Metabolic comorbidities, such as central obesity, type 2 diabetes, and dyslipidemia, are considered to be the risk factors most closely associated with MAFLD [54]. At present, the etiology and pathogenesis of this disease remains unclear, and Western medicine has yet to develop target-specific drugs. TCM has been proven to inhibit inflammatory pathways, regulate lipid production, improve insulin sensitivity, repair mitochondrial dysfunction, and promote the degeneration of liver cell autophagy (in the regulation of intestinal flora) and other pathways in the treatment of MAFLD. Saikosaponin, the main component of *Bupleuri Radix* is known to inhibit oxidative stress. It has been found to significantly reduce serum ALT, AST, TG, and fatty acid binding protein 4 levels in a high-fat diet-induced MAFLD mouse model by reducing endoplasmic reticulum stress stimulation-related proteins in fatty liver [55]. Astragaloside has also been found to inhibit lipid accumulation, oxidative stress, and the production of AST and ALT in AML-12 cells, reduce the expression of TNF-α and IL-10, and improve MAFLD [56]. The rosin extract dehydroabietic acid promoted the expression of Nrf2 downstream genes, such as HO-1, GSH, and GSH peroxidase 4, thereby eliminating the accumulation of ROS and reducing the lipid peroxide MDA levels in the liver. Further studies have shown that dehydroabietic acid can improve MAFLD by increasing the expression of key genes, such as ferroptosis suppressor protein 1, in vitro and in vivo, thereby inhibiting ferroptosis in hepatocytes [57]. Hesperetin, the active ingredient of *Citri Reticulatae Pericarpium*, alleviated liver steatosis, oxidative stress, inflammatory cell infiltration, and fibrosis by regulating the PI3K/AKT-Nrf2 signaling pathway; and further inhibited the NF-κB-mediated inflammatory response during the progression of MAFLD [58]. Kaempferol-3-O-glucuronide, a natural chemical constituent extracted from holly plants, has antioxidant, lipid metabolism-regulating, and anti-inflammatory properties. In a high-cholesterol diet-induced zebrafish model of MAFLD and an in vitro HepG2 cell model, kaempferol-3-O-glucuronide was found to protect cells from H_2O_2-induced liver injury, reduce MDA and neutrophil aggregation, increase GSH-Px by regulating the Nrf2/Keap1 signaling pathway, and play an antioxidant role, thereby ameliorating MAFLD [59]. AMPKα and PPARα are key regulators of lipid and glucose homeostasis; and the *Rhei Radix* et *Rhizoma* extract danthron significantly alleviated MAFLD by enhancing hepatic fatty acid oxidation, reducing lipid synthesis, and promoting mitochondrial homeostasis. Danthron may promote the combination of RXRα and PPARα, and enhance the binding of RXRα/PPARα heterodimer to adiponectin receptor 2 promoter, thereby activating the AMPKα and PPARα pathways [60]. Professor Rui-Xia Zhang, a famous Chinese medicine practitioner in Shaanxi Province, established a prescription of Huazhi Fugan granules (empirical formula, composed of *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Artemisiae Scopariae Herba*, *Alismatis Rhizoma*, *Scutellariae Radix*, and *Crataegi Fructus Alisma*) which can reduce the serum TC, TG, ALT, and AST levels in MCD-induced mice to alleviate hepatic steatosis. The mechanism was found to occur via the blocking of hepatocyte apoptosis, thereby reducing the levels of TNF-α and IL-1β to reduce inflammation and upregulating GSH-Px expression to alleviate oxidative stress [61]. The TCM Gegen Qinlian decoction (composed of *Puerariae Radix*, *Scutellariae Radix*, *Coptidis Rhizoma*, *a*nd *Glycyrrhizae Radix*) improves liver steatosis and injury in MAFLD, whose mechanism may be related to the regulation of inflammatory cytokines and anti-oxidative stress, as well as the inhibition of the activation of the NLRP3 signaling axis [62]. In terms of improving metabolism, the tomato extract tomatidine significantly inhibited the expression of fatty acid synthase and the transcription factors involved in lipogenesis, and increased the expression of adipose TG lipase. Further studies have shown that tomatidine can increase lipolysis and β-oxidation in fatty liver cells, which is associated with the upregulation of the SIRT1/AMPK signaling pathway [63]. Hyperoside, extracted from *Forsythiae Fructus*, has been found to attenuate MAFLD in rats via cholesterol and bile acid metabolism [64]. Similarly, the *Bupleuri Radix* extract saikosaponins reduced the expression of lipogenesis-related genes, such as diacylglycerol acyltransferase 2, glucose-6-phosphate dehydrogenase, malic enzyme 1, and diacylglycerol kinase alpha [65]. *Lonicerae Japonicae Flos* extract effectively reduced the levels of LDL, TG, and TC in the serum and the expression of the adipogenesis genes ACC-1, Fas, SREBP1, and PPARγ, as well as increased the expression of the fat-soluble genes CPT1, ATGL, LPL, and PPARα. In the HepG2 cell model, berberine, the main active component of *Coptidis Rhizoma*, was found to improve the Treg/Th17 ratio, liver pathological changes, and dyslipidemia in MAFLD rats by regulating the chemerin/CMKLR1 signaling pathway [66]. Professor Wei Zhou established Qihu preparation (composed of *Panax Notoginseng*, *Lonicerae Japonicae Flos*, *Dendrobii Caulis*, *Puerariae Thomsonii Radix*, *Astragali Radix*) and found that it improved fatty acid-induced hepatocyte swelling and steatosis in vitro by activating the AMPK/Txnip signaling pathway [3]. In terms of regulating the intestinal flora, the main active components of *Panax Ginseng* and *Panax Ginseng* saponins slowed down the transport of short-chain fatty acids from the intestine to the liver, inhibited TLR4 and the gut-liver axis Claudin-1 and ZO-1 proteins, and reduced AMPKα expression, thereby improving MAFLD [19]. *Panax Ginseng* reduced the release of pro-inflammatory factors by inhibiting the activation of the NF-κB/IκB signaling pathway, while promoting the expression of hepatic lipolysis genes (CPT-1a) and inhibiting the expression of lipogenesis genes (SREBP-1c, FAS, and ACC-1). Further studies have shown that total ginseng saponins can reduce MAFLD by modulating the gut microbiota, enhancing gut barrier function, and restoring energy balance [20]. Based on the TCM herbal formula of Buzhong Yiqi decoction (composed of *Astragali Radix*, *Panax Ginseng*, *Atractylodis Macrocephalae Rhizoma*, *Angelicae Sinensis Radix*, *Citri Reticulatae Pericarpium*, *Cimicifugae Rhizoma*, *Bupleuri Radix*, *Glycyrrhizae Radix*), Qinghua formula (composed of *Astragali Radix*, *Atractylodis Rhizoma*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*, *Panax Ginseng*, *Glycyrrhizae Radix*, *Angelicae Sinensis Radix*, *Smilacis Glabrae Rhizoma*), and has been found to alleviate liver dysfunction induced by high-fat diet in MAFLD rats. It also effectively reduced the degree of hepatic steatosis and regulated the abundance and composition of intestinal flora [4]. Chinese herbal medicine mixture 919 syrup (patent number: CN107929413B; composed of kiwifruit, *Sophorae Flavescentis Radix*, *Atractylodis Rhizoma*, *Sophorae Flavescentis Radix*, *Citri Reticulatae Pericarpium*, *Bupleuri Radix*) could reverse the abnormal expression of ghrelin pathway genes related to appetite in the brain and stomach and repair changes in the gut microbiota of MAFLD rat models [21]. The classic TCM prescription Si Miao formula (composed of *Atractylodis Rhizoma*, *Phellodendri Chinensis Cortex*, *Achyranthis Bidentatae Radix*, and *Coicis Semen*) downregulated the expression of lipid metabolism and inflammation-related factors in the liver tissue of MAFLD rats by increasing the proportion of *Akkermansia*, which significantly improved liver steatosis, insulin sensitivity, and glucose tolerance [22].

LF

LF is a chronic liver disease caused by the long-term stimulation of one or more physical, chemical, or microbial factors in the liver. Hepatic parenchymal cell damage eventually develops into liver cirrhosis and liver failure [67]. TCM has shown significant advantages in the treatment of LF and abnormal liver function by reducing transaminase levels and inhibiting the occurrence of inflammatory reactions. The main mechanisms include the inhibition of the activation of HSC, inhibition of the synthesis and degradation of the extracellular matrix, and inhibition of inflammation. Germacrone, extracted from *Curcumae Longae Rhizoma*, exerts antioxidant properties. In in vivo experiments in a rat model of LF induced by CCl_4, germacrone significantly improved liver tissue damage, as well as inhibited hepatic α-smooth muscle actin activity, HSC growth, and epithelial-mesenchymal transition progression. In in vitro experiments, germacrone significantly inhibited the survival and activation of TGF-β1-induced LX-2 cell model HSC by regulating the PI3K/AKT/mTOR signaling pathway and inducing apoptosis, thereby exerting an anti-hepatic fibrosis effect [68]. Phillygenin, a lignan isolated from *Forsythiae Fructus*, has potential anti-inflammatory and

anti-fibrotic effects. Through in vivo experiments, Wang et al. found that forsythin could improve abnormal liver function, histopathological damage, collagen deposition, inflammation, and fibrosis caused by CCl_4. Further studies have shown that phillygenin can restore the intestinal epithelial barrier and correct the imbalance of intestinal flora, thereby enriching the relative abundance of *Lactobacillus* [23]. Xiao et al. found that amygdalin could significantly reduce the content of hydroxyproline and the percentage of collagen-positive areas by inhibiting the TGF-β/Smad signaling pathway, thereby inhibiting HSC activation and LSEC dedifferentiation, and thus improving angiogenesis [69]. Schisandrin A improved thioacetamide-induced LF and TGF-β1-induced HSC-T6 cell activation in mice. The mechanism underlying this action may involve the inhibition the TGF-β1-mediated TAK1/MAPK pathway, resulting in the inhibition of HSC activation and the inflammatory response [70]. Saikosaponin, the main active component of *Bupleuri Radix*, reduced the expression levels of collagen and pro-fibrotic markers (COl1a1 and α-smooth muscle actin) and alleviated activation by inhibiting the NOD-like receptor family NLRP3 in fibrotic liver inflammation. Further in vitro studies showed that saikosaponin could inhibit the expression of pro-fibrotic markers and NLRP3 activation induced by TGF-β, and upregulate the expression of estrogen receptor-β [71]. Salidroside, the main component of the TCM *Rhodiolae Crenulatae Radix* et *Rhizoma*, alleviated mouse LF by inhibiting the migration, activation, and Akt phosphorylation of HSC induced by CXC chemokine ligand 16 [72]. Geniposide, the main active component of the TCM *Gardeniae Fructus*, reduced the serum liver enzyme levels, enhanced SOD and GSH-Px activity, and reduced the MDA levels. Similarly, geniposide has been found to increase the protein expression of B-cell lymphoma/leukemia-2, downregulate the protein expression of B-cell lymphoma/leukemia-2 associated protein, cleaved-caspase 3, and cleaved-caspase 9, and reduce hepatocyte apoptosis. Further serum non-targeted metabolomic analysis showed that geniposide treatment improved metabolic disorders, including glycerophospholipid, arginine and proline, and arachidonic acid metabolism [73]. Evodiamine, extracted from *Euodiae Fructus*, modulated the intestinal flora of mice with liver cirrhosis, including increasing the abundance of *Lactobacillus*, *Akkermansia*, and *Bacteroides* and reducing the abundance of *Enterococcus* and *Clostridium* [24]. Ligustroflavone, the active ingredient of *Chuanxiong Rhizoma*, reduced the pathological damage of liver tissue in mice and improved oxidative damage by downregulating the TGF-β/Smad signaling pathway [74]. Protocatechuic acid, extracted from *Catechu*, did not only inhibit the viability of TNF-α-activated HSC-T6 cells in vitro, but also effectively alleviated liver injury and fibrosis in vivo. Further experiments showed that protocatechuic acid could reduce the protein expression of p-Smad2, p-ERK, and c-Jun by regulating the TGF-β signaling pathway, thereby playing a role in the treatment of LF [75]. *Astragali Radix* significantly reduced serum liver function in rats, inhibited collagen deposition and HSC activation, and reduced inflammation. Further immunohistochemical analysis showed that *Astragali Radix* significantly inhibited LF by intervening with the inflammatory signaling pathway, mediated by high mobility group box 1 [5]. Physcion 8-O-β-glucopyranoside, an extract of *Rhei Radix* et *Rhizoma*, effectively improved rat LF and reduced collagen deposition. In vitro experiments have shown that physcion 8-O-β-glucopyranoside attenuates the inflammatory response by regulating the nuclear expression of NF-κB P65 mediated by sirtuin 3 in LF [76]. Genistein, a natural flavonoid mainly derived from soybean products (e.g., *Glycine max* (L.) Merr), has protective and anti-inflammatory effects on the liver and improves LF both in vivo and in vitro. Its mechanism involves the regulation of macrophages, whose functional properties are related to the inhibition of the JAK2/STAT3/SOCS3 signaling pathway [77]. *Cichorium pumilum* Jacq is a traditional herb used in Uighur medicine. Its extract, *Cichorium pumilum* Jacq ethyl acetate extract, improved LF in rats, caused by an abnormal intestinal gut-liver axis, by regulating the MAPK signaling pathway. The mechanism is exerted mainly by increasing the abundance of intestinal flora in hepatic fibrosis rat models, especially the ratio of *Firmicutes* and *Bacteroidetes*, which protects the intestinal mucosa of rats and improves the intestinal barrier function, thereby improving the gut-liver axis circulation and reducing liver inflammation [25]. Yiqi Huoxue recipe(composed of *Astragali Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Curcumae Longae Rhizoma*, *Smilacis Glabrae Rhizoma*, *Amomum kravanh Pierre* ex *Gagneop*) significantly reduced the morphological changes of LF and the expression level of LF markers in rats. Further research showed that Yiqi Huoxue significantly inhibited the activation of the TGF-β/Smad signaling pathway and downregulated the expression of Yes-associated protein, Tand connective tissue growth factor [6]. Fu et al. analyzed the anti-fibrotic components of Fuzheng Huayu recipe extract and developed a new formula composed of salvianolic acid B, schisandra A, and amygdalin, which they designated as the JY5 formula. This formulation significantly attenuated the CCl_4-induced hydroxyproline content and collagen deposition in LF in rats and mice, and inhibited HSC activation by inactivating Notch signaling both in vitro and in vivo [78]. In addition, Sun et al. evaluated the comprehensive anti-LF activity of each component of Fuzheng Huayu recipe, and screened seven ingredients (tanshinone II A, salvianolic acid B, cordycepin, amygdalin, quercetin, protopanaxatriol, and schizandrin B), which were recombined in equal proportions to form apobec complementation factor. A subsequent study confirmed that apobec complementation factor exerted a strong inhibitory effect on the activation of human HSC and the proliferation of human hepatic sinusoidal endothelial cells in vitro, and could effectively reduce the deposition of hepatic collagen in mice in vivo, thereby improving hepatic sinusoidal capillary vascularization [26]. The Baoganning formula, established by Professor Zhi-Ping Lyu, (composed of turtle shell, *Whitebackleaf Mallotus* Root, *Astragali Radix*, *Scutellariae Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*) effectively inhibited LF in mice and promoted T cell proliferation [7]. Ganshuang granules (CFDA approval number: Z20027671; mainly composed of *Bupleuri Radix*, *Paeoniae Alba Radix*, *Angelicae Sinensis Radix*, *Smilacis Glabrae Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, as well as 13 other drugs) significantly reduced the liver index, and ALT and AST levels in a mouse model of LF, as well as attenuated oxidative stress, inflammation, and LF. Furthermore, 16S rRNA sequencing has shown that Ganshuang granules can improve the α- and β-diversity of the intestinal flora, reduce the ratio of *Firmicutes* to *Bacteroidetes*, and regulate the relative abundance of various bacteria [79]. Ziqi decoction inhibited the activation of TLR4-related NF-κB signaling pathway and the nuclear translocation of activated NF-κB, while simultaneously inhibiting the MAPK signaling pathway, thereby preventing the activation of HSC [80].

HCC

HCC can be divided into two categories: primary and secondary HCC. The incidence of primary liver cancer is very high, and Western medicine treatment methods have yet to address their numerous disadvantages, including side effects, high price, and drug resistance. Therefore, there is an urgent need to develop safe and effective anti-HCC agents. The use of TCM for the treatment of liver cancer has significant advantages in terms of the inhibition of tumor cell proliferation, improvement of the immune system, and increased patient survival rates. The deletion of the WW domain-containing oxidoreductase is associated with malignant metastasis in patients with HCC. In this context, Yang et al. screened 19,050 human genes based on the CRISPR genome-wide knockout library and found that the main active component of *Toosendan Fructus* is a WW domain-containing oxidoreductase agonist. By evaluating in vivo and in vitro models of WW domain-containing oxidoreductase overexpression and knockout using toosendanin, they found that toosendanin activated WW domain-containing oxidoreductase transduction via the JAK2/STAT3 and Wnt/β-catenin signaling pathways, thereby effectively inhibiting the metastasis of HCC [81]. Furthermore, 5-hydroxytryptamine (serotonin) receptor 1D significantly promoted the proliferation, colony formation, migration,

and invasion of HepG2 and SMMC-7721 cells, and increased the expression of Wnt/β-catenin pathway-related proteins. Paeoniflorin, an active ingredient of *Paeonia lactiflora* Pall., affected HCC progression by inhibiting the Wnt/β-catenin pathway via the downregulation of 5-hydroxytryptamine (serotonin) receptor 1D expression [82]. Similarly, artesunate, an extract of *Artemisiae Annuae Herba*, significantly enhanced the anticancer effect of sorafenib on Huh7, SNU-449, and SNU-182 HCC cells in a Balb/c mouse Huh7 cell xenograft model, whose main effect was exerted in lysosomes; synergistically with sorafenib, artesunate was also found to exacerbate lipid peroxidation and ferroptosis [83]. Chrysin, a flavonoid extracted from *Oroxyli Semen*, effectively inhibited tumor progression while increasing the proportion of CD4/CD8 + T cells in the tumor tissues of the H22 xenograft mouse model. Furthermore, chrysin significantly downregulated programmed cell death ligand 1 expression by blocking the STAT3 and NF-κB pathways both in vivo and in vitro. In a co-culture system of HepG2 and Jurkat T cells, chrysin increased the proliferation of T cells and the concentration of IL-2. Cofilin 1 is highly expressed in patients with HCC and is known to affect HCC metastasis via the cofilin 1/F-actin axis [84]. Nujiangexanthone A, a flavonoid isolated from *Garcinia cambogia*, effectively inhibited the migration, invasion, and metastasis of HCC cells in vitro and in vivo by downregulating the expression of cofilin 1 [85]. Trilobolide-6-O-isobutyrate, isolated from *Trifolium* spp, induced HCC cell cycle arrest in the G2/M phase, mitochondrial caspase-dependent apoptosis, and glycolysis, thereby significantly inhibiting HCC cell migration and invasion. Further studies showed that trilobolide-6-O-isobutyrate could inhibit the activation of the STAT3 pathway by directly interacting with the TYR 640/657 sites of STAT3 protein and reducing STAT3 level. Moreover, ilobolide-6-O-isobutyrate regulated the expression of proliferating cell nuclear antigen, antigen KI-67, CCNB1, cyclin E, B-cell lymphoma/leukemia-2 associated protein and B-cell lymphoma-2 (Bcl2), by inhibiting the IL-6/STAT3 signaling pathway, thereby effectively eliminating tumor growth without damaging healthy tissues [86]. Homoharringtonine, isolated from the bark of *Torreya chinensis*, was used to treat a nude mouse xenograft model in an in vivo study; the results showed that homoharringtonine significantly reduced the index of tumor size, angiogenesis, and stiffness, thereby exerting a strong tumor inhibitory effect. In vitro studies have shown that homoharringtonine can effectively inhibit the proliferation, migration, invasion, and epithelial-mesenchymal transition of HCC cells via the PI3K/AKT/GSK3β/Slug signaling pathways, as well as induce cell cycle arrest in the G2 phase and apoptosis, thereby inhibiting the proliferation of HCC cells [87]. Guo prepared nanocarriers by combining the advantages of natural polysaccharides (*Angelicae Sinensis Radix* polysaccharide) and natural Chinese medicine (*Curcumin*) to design functionalized nanoparticles with the aim of improving therapeutics via cell membrane encapsulation and immunotherapy. The nanocarriers enhanced the effect of targeted therapy and increased the expression of IL-12, TNF-α, interferon-γ, and CD8 + T cell infiltration via immunomodulatory effects, with high levels of anti-liver cancer efficiency and targeting ability [88]. Using network pharmacology analysis, Li et al. identified five bioactive compounds in the TCM Huanglian decoction (composed of *Coptidis Rhizoma*, *Zingiberis Rhizoma*, *Artemisiae Argyi Folium*, and *Mume Fructus*) that act on HCC. They identified CCNB1 gene as a potential therapeutic target for HCC. The Huanglian decoction was used to treat a CCNB1 knockout model in vitro, and significantly inhibited the growth, migration, and invasion of HCC cells. Further studies have shown that Huanglian decoction can inhibit the growth of HCC cells by downregulating CCNB1 expression and activating the p53 signaling pathway [89]. Shen et al. used a well-known TCM, Yanggan Huayu granules (composed of *Broussonetiae Fructus*, *Curcumae Rhizoma*, and *Lycopi Herba*), to treat a H22 mouse xenograft model and found that it effectively inhibited tumor volume and weight, and induced apoptosis in HepG2 and SMMC-7721 cells, increased the protein expression of cleaved-caspase3 and cleaved poly ADP-ribose polymerase, and downregulated the protein expression of phosphorylated AKT protein, thereby inhibiting the growth of HCC cells [90]. Kang-ai injection (CFDA approval number: Z20026868; composed of *Panax Ginseng*, *Astragali Radix*, and *Sophorae Flavescentis Radix*) improved immune function, induced tumor cell apoptosis, and inhibited tumor cell proliferation, invasion, and metastasis. Sun et al. analyzed data obtained from 35 trials involving 2,501 patients with HCC and found that Kang-ai injection effectively alleviated several of the adverse reactions caused by conventional treatment, including nausea and vomiting, liver injury, peripheral neurotoxicity, fever, abdominal pain, hair loss, increased bilirubin level, leukopenia, and decreased hemoglobin levels, and effectively improved the objective remission rate and disease control rate, thereby improving the quality of life [8].

CLD

CLD is caused by a variety of factors and is characterized by cholestasis, accompanied by changes in the polarity of hepatocytes and an imbalance in bile acid homeostasis. CLD has a high clinical incidence, complex etiology and an unclear pathogenesis [91]. At present, TCM has attracted much attention in the prevention and treatment of CLD, and its mechanism of action has been found to involve the farnesoid X receptor (FXR) and constitutive androstane receptor pathways. Tectorigenin, an isoflavone extracted from the dried flowers of *Puerariae Radix*, promoted the expression of bile transporters and enhanced the output of bile acids by inhibiting the recruitment and activation of hepatic macrophages and by activating the PPARγ pathway, thereby alleviating intrahepatic cholestasis [92]. FXR is a novel target for the treatment of CLD. Sirtuin 1 (SIRT1) is a sirtuin that promotes FXR activity by its deacetylation. Pterostilbene, the active ingredient of *Santali Albi Lignum*, is an activator of SIRT1 and can inhibit the infiltration and activation of mouse liver macrophages through the SIRT1-p53 signaling pathway, as well as inhibit the infiltration and activation of mouse liver macrophages through the SIRT1-FXR signaling pathway, thereby improving hepatic bile metabolism [93]. In addition, arbutin, the active ingredient of *Uva ursi*, also alleviated α-naphthyl isothiocyanate-induced bile by upregulating the FXR levels and downstream enzymes related to bile acid homeostasis, including bile salt export pump, normal tissue complication probability and sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone-preferring, member 1 [94]. The TCM herbal formula Huangqi decoction (composed of Huangqi decoction: classical formula, composition by *Astragali Radix*, *Sesamum Indicum*, white honey, and *Citri Reticulatae Pericarpium*) and astragaloside, the active component of *Astragali Radix*, improved bile acid and free fatty acid metabolism by regulating bile acid transporters, nuclear hormone receptors, and membrane receptors, and reduced α-naphthyl isothiocyanate-induced serum bile acid and free fatty acid levels in a rat model, thereby improving liver function impairment, histopathological abnormalities, and lipid peroxidation damage [9]. In a mouse model of chronic cholestasis, Da-Huang-Xiao-Shi decoction (composed of *Phellodendri Chinensis Cortex*, *Rhei Radix* et *Rhizoma*, *Glauber's salt*, and *Gardeniae Fructus*) significantly reduced serum biochemical indices, improved liver pathological damage, and relieved bile acid in vivo by increasing the expression of bile acid-related metabolic enzymes and efflux transporter homeostasis [95]. Using 16S rDNA sequencing, Zhuyu pill (composed of *Coptidis Rhizoma*, *Euodiae Fructus* at a dosage ratio of 1:1) was found to exert a significant anti-cholestasis effect by restoring the imbalance of intestinal flora and increasing the abundance of beneficial bacteria (*Bacteroidetes*, *Lactobacillus*, and *Actinobacteria*) and pathogenic bacteria (*Gammaproteoba cteria*). Metabolomics analysis also showed that Zhuyu pills prevented cholestasis by improving amino acid metabolism, steroid hormone biosynthesis, and bile secretion [27].

Other liver diseases

Autoimmune hepatitis is a chronic inflammatory liver disease that poses a significant threat to human health worldwide. In this context, formononetin is a natural herbal extract that has various biological

functions. In a mouse model of autoimmune hepatitis induced by concanavalin A, formononetin, an extract of *Spatholobus suberctu*, greatly reduced the levels of pro-inflammatory cytokines in the serum and liver tissue of mice, consequently downregulating the expression of pro-apoptotic proteins (e.g., B-cell lymphoma/leukemia-2 associated protein, cleaved caspase 9, and cleaved caspase 3), and upregulating the expression of anti-apoptotic proteins. Additionally, formononetin inhibited the activation of the NF-κB signaling pathway and NLRP3 inflammasome. Therefore, formononetin could be a potential drug for the treatment of autoimmune hepatitis [96]. Magnesium isoglycyrrhizinate, a recently discovered glycyrrhizin that is extracted from *Glycyrrhizae Radix*, exerted significant effects in a concanavalin A-induced immune liver injury mouse model, wherein it significantly improved the survival rate of mice and ameliorated concanavalin A-induced immune liver injury by inhibiting hepatic autophagy [97].

Hepatic encephalopathy is a central nervous system syndrome characterized by metabolic dysfunction caused by severe liver disease. Inhibition of TLR-4 related inflammation can effectively improve neurocognitive dysfunction in mild hepatic encephalopathy [98]. A clinical randomized controlled study of 62 patients showed that Babaodan (CFDA approval number: Z10940006; composed of *Bos taurus domesticus Gmelin*, *Python molurus bivittatus Schlegel*, *Panax Ginseng*, and *Moschus*) combined with lactulose could reduce number connection test A and increase digit symbol test, significantly improving neurocognitive function, suppressing systemic inflammation, and improving liver function by reducing inflammatory factors, and the levels of ammonia, ALT, AST, and total bilirubin. In vitro studies have shown that Babaodan significantly reduces primary bone marrow derived macrophages/peritoneal macrophages in rats and primary primary bone marrow derived macrophages/peritoneal macrophages/microglia/astrocytes in mice by regulating the expression of IL-1β, IL-6 and TNF-α via the P65, JNK, ERK, and P38 signaling pathways. Similarly, in vivo studies have shown that Babaodan reduces the mortality of mice with endotoxemia, and further reduces the levels of ALT, AST, IL-1β, and inflammatory factors, thereby improving liver tissue damage [99]. In a rat model of hepatic encephalopathy induced by CCl_4 and thioacetamide, electroacupuncture significantly improved brain tissue necrosis and nuclear pyknosis while decreasing the levels of ALT, AST, total bilirubin, and total bile acid. The mechanism underlying the inhibition of the production of pro-inflammatory cytokines may be related to the downregulation of the p38MAPK/STAT3 and TLR4/MyD88/NF-κB signaling pathways [100].

Chronic liver failure is a complication of cirrhosis characterized by a progressive decline and decompensation of liver function. Recently, TCM has played an important role in the treatment of liver failure. Fuyang Jiedu Huayu granules (composed of *Aconitum carmichaeli Debx*, *Paeoniae Rubra Radix*, *Panax Ginseng*, *Rhei Radix* et *Rhizoma*, and *Artemisiae Argyi Folium*) reduced the serum ALT, AST, and total bilirubin levels in a CCl_4-induced rat chronic liver failure model, and reduced liver tissue damage and pathological damage, increased the expression of GRB2-associated binding protein 1 and its receptor in liver tissue, promoted angiogenesis, and improved hematopoietic function, thereby relieving chronic liver failure [101].

Conclusion and future perspective

In 2021, significant progress was made in the research on TCM monomers, their extracts, and TCM compounds in the treatment of liver diseases, demonstrating the potential advantages and considerable development prospects of TCM in the field of medicine. TCM can be used to prevent and treat liver diseases via a variety of mechanisms, including the regulation of lipid metabolism, anti-liver injury, anti-oxidative stress, bile acid metabolism, the immune system, anti-hepatitis virus replication, and anti-liver cancer proliferation. In the past year, metabolomics, transcriptomics, network pharmacology, 16S rRNA gene sequencing, and other omics analyses have been used in TCM research. Additionally, network pharmacology combined with systems biology, multi-faceted pharmacology, bioinformatics, and other disciplines have created new opportunities to address the complexities of TCM research based on the "disease-gene-target-drug" interaction network. This theory can provide systematic perspectives for future research on the mechanism of TCM [102].

In the future, screening for more effective ingredients and studies on their molecular mechanisms will need to be strengthened [103]. For example, recent studies have shown that ferroptosis plays a non-negligible role in the regulation of multiple pathological progressions in the liver, and excess iron may be cytotoxic, leading to hepatocyte death and inducing diseases, such as metabolic-related fatty liver. In addition, we now know that changes in intestinal flora and intestinal permeability can further affect the development of liver disease via the gut-liver axis. The mechanisms underlying these effects should be elucidated and referenced in future research on the treatment of liver diseases using TCM. Ethnic medicine, a category of medicine to which TCM belongs, is clearly indispensable in the treatment of liver diseases.

This is a comprehensive review of the latest research on the prevention and treatment of liver disease using TCM in 2021, summarizing key information on the effects of TCM compounds on a range of diseases (Table 4). As such, this review provides a scientific and effective reference for the treatment of liver disease and a solid foundation for further TCM-based liver disease research.

Table 4 Important compound information

Compound	Original rource	Molecular formula	Pubchem CID	Molecule wight (g/mol)	Reference
Amygdalin	*Armeniacae Semen Amarum*	$C_{20}H_{27}NO_{11}$	656516	457.40	[32]
Dicoumarol	*Medicago sativa* L.	$C_{19}H_{12}O_6$	54676038	336.30	[33]
Quercetin	*Albiziae Cortex*	$C_{15}H_{10}O_7$	5280343	302.23	[38]
Kushenin	*Sophorae Flavescentis Radix*	$C_{15}H_{24}N_2O_2$	114850	286.28	[39]
Lupeol	Olive	$C_{39}H_{56}O$	5471662	426.70	[43]
Luteolin	*Chrysanthemi Indici Flos*	$C_{15}H_{10}O_6$	5280045	286.24	[46]
Schizandrin A	*Schisandrae Chinensis Fructus*	$C_{24}H_{32}O_6$	155256	416.50	[46]
Schizandrin B	*Schisandrae Chinensis Fructus*	$C_{23}H_{28}O_6$	108130	400.50	[46]
Astragaloside	*Astragali Radix*	$C_{28}H_{32}O_{17}$	5488387	640.50	[2]
Puerarin	*Puerariae Radix*	$C_{21}H_{20}O_9$	5281807	416.40	[49]
Saikosaponin	*Bupleuri Radix*	$C_{42}H_{68}O_{13}$	44202893	781.00	[57]
Dehydroabietic acid	Rosin	$C_{20}H_{28}O_2$	94391	300.40	[58]
Hesperetin	*Citri Reticulatae Pericarpium*	$C_{16}H_{14}O_6$	72281	302.28	[60]
Danthron	*Rhei Radix* et *Rhizoma*	$C_{14}H_8O_4$	2950	240.21	[61]

Table 4 Important compound information (*continued*)

Compound	Original rource	Molecular formula	Pubchem CID	Molecule wight (g/mol)	Reference
Germacrone	*Curcumae Longae Rhizoma*	$C_{15}H_{22}O$	6436348	218.33	[68]
Berberine	*Coptidis Rhizoma*	$C_{20}H_{18}NO_4$	336.4	336.40	[66]
Forsythin	*Forsythiae Fructus*	$C_{29}H_{36}O_{15}$	5281773	457.40	[23]
Rhodioloside	*Rhodiolae Crenulatae Radix* et *Rhizoma*	$C_{14}H_{20}O_7$	159278	300.30	[72]
Geniposide	*Gardeniae Fructus*	$C_{17}H_{24}O_{10}$	107848	388.40	[73]
Evodiamine	*Euodiae Fructus*	$C_{19}H_{17}N_3O$	442088	303.40	[24]
Ligustroflavone	*Chuanxiong Rhizoma*	$C_{33}H_{40}O_{18}$	10417462	724.70	[74]
Protocatechuic acid	*Catechu*	$C_{13}H_{16}O_9$	91309592	154.12	[75]
Genistein	*Glycine max* (L.) Merr.	$C_{15}H_{10}O_5$	5280961	270.24	[77]
Salvianolic acid B	*Salviae Miltiorrhizae Radix* et *Rhizoma*	$C_{36}H_{30}O_{16}$	11629084	718.60	[78]
Tanshinone II A	*Salviae Miltiorrhizae Radix* et *Rhizoma*	$C_{19}H_{18}O_3$	164676	294.30	[79]
Cordycepin	*Cordyceps*	$C_{10}H_{13}N_5O_3$	6303	251.24	[79]
Toosendanin	Neem	$C_{30}H_{38}O_{11}$	9851101	574.60	[81]
Paeoniflorin	*Paeoniae Alba Radix*	$C_{23}H_{28}O_{11}$	442534	480.50	[82]
Artesunate	*Artemisiae Annuae Herba*	$C_{19}H_{28}O_8$	6917864	384.40	[83]
Chrysin	*Oroxyli Semen*	$C_{15}H_{10}O_4$	5281607	254.24	[84]
Curcumin	*Curcumae Longae Rhizoma*	$C_{21}H_{20}O_6$	969516	368.40	[88]
Tectorigenin	*Puerariae Radix*	$C_{16}H_{12}O_6$	5281811	300.26	[92]
Pterostilbene	*Santali Albi Lignum*	$C_{16}H_{16}O_3$	5281727	256.30	[93]
Arbutin	Uva ursi	$C_{12}H_{16}O_7$	440936	272.25	[94]
Formononetin	*Ononis Spinosa*	$C_{16}H_{12}O_4$	5280378	268.26	[96]
Magnesium isoglycyrrhizinate	*Glycyrrhizae Radix*	$C_{84}H_{118}Mg_3O_{32}$	139032961	1,712.70	[97]

References

1. Fu K, Wang C, Ma C, Zhou H, Li Y. The potential application of Chinese medicine in liver diseases: a new ppportunity. *Front Pharmacol*. 2021;12:771459. https://doi.org/10.3389/fphar.2021.771459
2. Jiang ZB, Gao J, Chai YH, Li W, Luo YF, Chen YZ. Astragaloside alleviates alcoholic fatty liver disease by suppressing oxidative stress. *Kaohsiung J Med Sci*. 2021;37(8):718–729. https://doi.org/10.1002/kjm2.12390
3. Zeng H, Li X, Zhou D, et al. Qihu preparation ameliorates diabetes by activating the AMPK signaling pathway in db/db mice. *Diabetes Metab Syndr Obes*. 2021;14:3229–3241. https://doi.org/10.2147/DMSO.S312137
4. Wang Y, Lv S, Shen T, et al. Qinghua Fang inhibits high-fat diet-induced non-alcoholic fatty liver disease by modulating gut microbiota. *Ann Palliat Med*. 2021;10(3):3219–3234. https://doi.org/10.21037/apm-21-448
5. Wen J, Wang D, Wang J, Wang R, Wei S, Zhao Y. *Astragali Radix* contributes to the inhibition of liver fibrosis via high-mobility group box 1-mediated inflammatory signaling pathway. *Evid Based Complement Alternat Med*. 2021;2021:5574010. https://doi.org/10.1155/2021/5574010
6. Zhao W, Zhang X, Hou M, et al. Traditional Chinese medicine Yiqi Huoxue recipe attenuates hepatic fibrosis via YAP/TAZ signaling. *Histol Histopathol*. 2021;36(9):967–979. https://doi.org/10.14670/HH-18-373
7. Mo C, Xie S, Gao L, Lü Z. Baoganning formula alleviates liver fibrosis in mice by inhibiting hepatic IDO1 expression and promoting phenotypic maturation of dendritic cells. *J South Med Univ*. 2021;41(7):1002–1011. (Chinese). https://doi.org/10.12122/j.issn.1673-4254.2021.07.06
8. Shen Y, Yang F, Peng H, et al. Anti-tumor effect of Yanggan Huayu granule by inducing AKT-mediated apoptosis in hepatocellular carcinoma. *J Ethnopharmacol*. 2022;282:114601. https://doi.org/10.1016/j.jep.2021.114601
9. Qiu J, Yan J, Liu W, et al. Metabolomics analysis delineates the therapeutic effects of Huangqi decoction and astragalosides on α-naphthylisothiocyanate (ANIT)-induced cholestasis in rats. *J Ethnopharmacol*. 2021;268:113658. https://doi.org/10.1016/j.jep.2020.113658
10. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. *J Hepatol*. 2020;72(3):558–577. https://doi.org/10.1016/j.jhep.2019.10.003
11. Milosevic I, Vujovic A, Barac A, et al. gut-liver axis, gut microbiota, and its modulation in the management of liver diseases: a review of the literature. *Int J Mol Sci*. 2019;20(2):395. https://doi.org/10.3390/ijms20020395
12. Svegliati-Baroni G, Patrício B, Lioci G, Macedo MP, Gastaldelli A. Gut-pancreas-liver axis as a target for treatment of NAFLD/NASH. *Int J Mol Sci*. 2020;21(16):5820. https://doi.org/10.3390/ijms21165820
13. Bajaj JS. Alcohol, liver disease and the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2019;16(4):235–246. https://doi.org/10.1038/s41575-018-0099-1
14. Juneja P, Tripathi DM, Kaur S. Revisiting the gut-liver axis: gut lymphatic system in liver cirrhosis and portal hypertension [published online Feb 23, 2022]. *Am J Physiol Gastrointest Liver Physiol*. 2022. https://doi.org/10.1152/ajpgi.00271.2021
15. Ran B, Guo CE, Li W, et al. Sea buckthorn (*Hippophae rhamnoides* L.) fermentation liquid protects against alcoholic liver disease linked to regulation of liver metabolome and the abundance of gut microbiota. *J Sci Food Agric*. 2021;101(7):2846–2854. https://doi.org/10.1002/jsfa.10915
16. Yu H, Liu C, Zhang F, et al. Efficacy of Zhuyu pill intervention in

a cholestasis rat model: mutual effects on fecal metabolism and microbial diversity. *Front Pharmacol*. 2021;12:695035. https://doi.org/10.3389/fphar.2021.695035
17. Yu H, Liu C, Wang J, et al. miRNA and miRNA target genes in intervention effect of Zhuyu pill on cholestatic rat model. *J Ethnopharmacol*. 2022;283:114709. https://doi.org/10.1016/j.jep.2021.114709
18. Xu L, Huang Q, Tan X, et al. Patchouli alcohol ameliorates acute liver injury via inhibiting oxidative stress and gut-origin LPS leakage in rats. *Int Immunopharmacol*. 2021;98:107897. https://doi.org/10.1016/j.intimp.2021.107897
19. Xu Y, Wang N, Tan HY, Li S, Zhang C, Feng Y. Gut-liver axis modulation of *Panax notoginseng* saponins in nonalcoholic fatty liver disease. *Hepatol Int*. 2021;15(2):350–365. https://doi.org/10.1007/s12072-021-10138-1
20. Liang W, Zhou K, Jian P, et al. Ginsenosides improve nonalcoholic fatty liver disease via integrated regulation of gut microbiota, inflammation and energy homeostasis. *Front Pharmacol*. 2021;12:622841. https://doi.org/10.3389/fphar.2021.622841
21. Chen M, Xing J, Pan D, Gao P. Effect of Chinese herbal medicine mixture 919 syrup on regulation of the ghrelin pathway and intestinal microbiota in rats with non-alcoholic fatty liver disease. *Front Microbiol*. 2021;12:793854. https://doi.org/10.3389/fmicb.2021.793854
22. Han R, Qiu H, Zhong J, et al. Si Miao formula attenuates non-alcoholic fatty liver disease by modulating hepatic lipid metabolism and gut microbiota. *Phytomedicine*. 2021;85:153544. https://doi.org/10.1016/j.phymed.2021.153544
23. Wang C, Ma C, Fu K, et al. Phillygenin attenuates carbon tetrachloride-induced liver fibrosis via modulating inflammation and gut microbiota. *Front Pharmacol*. 2021;12:756924. https://doi.org/10.3389/fphar.2021.756924
24. Miao J, Cui HT, Wang L, et al. Effects of evodiamine on carbon tetrachloride-induced liver fibrosis mice based on modulating gut microbiota. *Chin J Ind Hyg Occup Dis*. 2021;39(6):401–406. (Chinese) https://doi.org/10.3760/cma.j.cn121094-20201204-00666
25. Han C, Wu X, Zou N, et al. *Cichorium pumilum* Jacq extract inhibits LPS-induced inflammation via MAPK signaling pathway and protects rats from hepatic fibrosis caused by abnormalities in the gut-liver axis. *Front Pharmacol*. 2021;12:683613. https://doi.org/10.3389/fphar.2021.683613
26. Sun X, Tan Y, Lyu J, Liu HL, Zhao ZM, Liu CH. Active components formulation developed from Fuzheng Huayu recipe for anti-liver fibrosis [published online Sep 28, 2021]. *Chin J Integr Med*. 2021. https://doi.org/10.1007/s11655-021-3293-x
27. Yu H, Liu C, Zhang F, et al. Efficacy of Zhuyu pill intervention in a cholestasis rat model: mutual effects on fecal metabolism and microbial diversity. *Front Pharmacol*. 2021;12:695035. https://doi.org/10.3389/fphar.2021.695035
28. Soret PA, Magusto J, Housset C, Gautheron J. In vitro and in vivo models of non-alcoholic fatty liver disease: a critical appraisal. *J Clin Med*. 2020;10(1):36. https://doi.org/10.3390/jcm10010036
29. Saviano A, Henderson NC, Baumert TF. Single-cell genomics and spatial transcriptomics: discovery of novel cell states and cellular interactions in liver physiology and disease biology. *J Hepatol*. 2020;73(5):1219–1230. https://doi.org/10.1016/j.jhep.2020.06.004
30. Li M, Shang H, Wang T, et al. Huanglian decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression. *World J Gastroenterol*. 2021;27(10):939–958. https://doi.org/10.3748/wjg.v27.i10.939
31. Li Z, Li Y, Li X, et al. Statins in hepatitis B or C patients is associated with reduced hepatocellular carcinoma risk: a systematic review and meta-analysis [published online Feb 4, 2022]. *Turk J Gastroenterol*. 2022. https://doi.org/10.5152/tjg.2020.19656
32. Wang R, Zhang D, Sun K, et al. Amygdalin promotes the activity of T cells to suppress the progression of HBV-related hepatocellular carcinoma via the JAK2/STAT3 signaling pathway. *BMC Infect Dis*. 2021;21(1):56. https://doi.org/10.1186/s12879-020-05713-0
33. Cheng ST, Hu JL, Ren JH, et al. Dicoumarol, an NQO1 inhibitor, blocks cccDNA transcription by promoting degradation of HBx. *J Hepatol*. 2021;74(3):522–534. https://doi.org/10.1016/j.jhep.2020.09.019
34. Rahman MA, Ueda K, Honda T. A traditional Chinese medicine, maoto, suppresses hepatitis B virus production. *Front Cell Infect Microbiol*. 2021;10:581345. https://doi.org/10.3389/fcimb.2020.581345
35. Xu T, Wang P, Zheng X, et al. The therapeutic effects and mechanisms of Long Chai Fang on chronic hepatitis B. *Ann Transl Med*. 2021;9(10):865. https://doi.org/10.21037/atm-21-1923
36. Ge FL, Si LL, Yang Y, et al. Chinese patent medicine Liuweiwuling tablet had potent inhibitory effects on both wild-type and entecavir-resistant hepatitis B virus (HBV) in vitro and effectively suppressed HBV replication in mouse model. *Front Pharmacol*. 2021;12:756975. https://doi.org/10.3389/fphar.2021.756975
37. Chen TY, Mai JY, Zhang P, et al. Efficacy of Erzhu Jiedu recipe on hepatitis B cirrhosis with hyperalphafetoproteinemia: a randomized, double-blind, placebo-controlled clinical trial. *Medicine* (*Baltimore*). 2021;100(38):e27231. https://doi.org/10.1097/MD.0000000000027231
38. He A, Wang W, Xia Y, Niu X. A network pharmacology approach to explore the mechanisms of *Artemisiae scopariae* herba for the treatment of chronic hepatitis B. *Evid Based Complement Alternat Med*. 2021;2021:6614039. https://doi.org/10.1155/2021/6614039
39. Liao Q, Wen J, Jiang K, Zhao Y, Ma X. Kushenin combined with adefovir dipivoxil or entecavir for chronic hepatitis B: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2021;2021:8856319. https://doi.org/10.1155/2021/8856319
40. Xiong W, Yuan Z, Wang T, et al. Quercitrin attenuates acetaminophen-induced acute liver injury by maintaining mitochondrial complex I activity. *Front Pharmacol*. 2021;12:586010. https://doi.org/10.3389/fphar.2021.586010
41. Xu S, Kong F, Sun Z, Xi Y, Qi F, Sun J. Hepatoprotective effect and metabonomics studies of radix gentianae in rats with acute liver injury. *Pharm Biol*. 2021;59(1):1172–1180. https://doi.org/10.1080/13880209.2021.1969414
42. Zheng Y, Lei L, Liang S, et al. Protective effect of fresh/dry dandelion extracts on APAP-overdose-induced acute liver injury [published online Nov 24, 2021]. *Chin J Integr Med*. 2021. https://doi.org/10.1007/s11655-021-3295-8
43. Huang S, Mo C, Zeng T, et al. Lupeol ameliorates LPS/D-GalN induced acute hepatic damage by suppressing inflammation and oxidative stress through TGFβ1-Nrf2 signal pathway. *Aging* (*Albany NY*). 2021;13(5):6592–6605. https://doi.org/10.18632/aging.202409
44. Yu HH, Qiu YX, Li B, Peng CY, Zeng R, Wang W. *Kadsura heteroclita* stem ethanol extract protects against carbon tetrachloride-induced liver injury in mice via suppression of oxidative stress, inflammation, and apoptosis. *J Ethnopharmacol*. 2021;267:113496. https://doi.org/10.1016/j.jep.2020.113496
45. Xie SZ, Zhai XY, Xi SY, et al. The protective effects of *Zornia diphylla* (L.) Pers. against acute liver injury induced by carbon tetrachloride in mice. *Front Pharmacol*. 2021;12:764282. https://doi.org/10.3389/fphar.2021.764282
46. Gao Y, Shi W, Yao H, et al. An integrative pharmacology based

analysis of refined Liuweiwuling against liver injury: a novel component combination and hepaprotective mechanism. *Front Pharmacol*. 2021;12:747010. https://doi.org/10.3389/fphar.2021.747010
47. Cao L, Li Z, Ren Y, et al. Xuebijing protects against septic acute liver injury based on regulation of GSK-3β pathway. *Front Pharmacol*. 2021;12:627716. https://doi.org/10.3389/fphar.2021.627716
48. Ji Y, Si W, Zeng J, et al. Niujiaodihuang detoxify decoction inhibits ferroptosis by enhancing glutathione synthesis in acute liver failure models. *J Ethnopharmacol*. 2021;279:114305. https://doi.org/10.1016/j.jep.2021.114305
49. Liu YS, Yuan MH, Zhang CY, et al. *Puerariae Lobatae* radix flavonoids and puerarin alleviate alcoholic liver injury in zebrafish by regulating alcohol and lipid metabolism. *Biomed Pharmacother*. 2021;134:111121. https://doi.org/10.1016/j.biopha.2020.111121
50. Bian L, Chen H, Zhou X. Untargeted lipidomics analysis of *Mori Fructus* polysaccharide on acute alcoholic liver injury in mice using ultra performance liquid chromatography-quadrupole-orbitrap-high resolution mass spectrometry. *Int Immunopharmacol*. 2021;97:107521. https://doi.org/10.1016/j.intimp.2021.107521
51. Liang HW, Yang TY, Teng CS, et al. Mulberry leaves extract ameliorates alcohol-induced liver damages through reduction of acetaldehyde toxicity and inhibition of apoptosis caused by oxidative stress signals. *Int J Med Sci*. 2021;18(1):53–64. https://doi.org/10.7150/ijms.50174
52. Je J, Kim H, Park EJ, et al. Fermentation of sprouted ginseng (*Panax Ginseng*) increases flavonoid and phenolic contents to attenuate alcoholic hangover and acute liver injury in mice. *Am J Chin Med*. 2021;49(1):131–146. https://doi.org/10.1142/S0192415X21500075
53. Ye S, Ren LL, Chen X, et al. Protective effect and mechanism of Wangshi Baochi pills against acute alcoholic liver/stomach injury in mice. *China J Chin Mater Med*. 2021;46(15): 3900–3906. (Chinese) https://doi.org/10.19540/j.cnki.cjcmm.20210408.401
54. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397(10290):2212–2224. https://doi.org/10.1016/S0140-6736(20)32511-3
55. Chang GR, Lin WL, Lin TC, Liao HJ, Lu YW. The ameliorative effects of saikosaponin in thioacetamide-induced liver injury and non-alcoholic fatty liver disease in mice. *Int J Mol Sci*. 2021;22(21):11383. https://doi.org/10.3390/ijms222111383
56. Hu Q, Zhang W, Wu Z, et al. Baicalin and the liver-gut system: pharmacological bases explaining its therapeutic effects. *Pharmacol Res*. 2021;165:105444. https://doi.org/10.1016/j.phrs.2021.105444
57. Gao G, Xie Z, Li EW, et al. Dehydroabietic acid improves nonalcoholic fatty liver disease through activating the Keap1/Nrf2-ARE signaling pathway to reduce ferroptosis. *J Nat Med*. 2021;75(3):540–552. https://doi.org/10.1007/s11418-021-01491-4
58. Li J, Wang T, Liu P, et al. Hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD. *Food Funct*. 2021;12(9): 3898–3918. https://doi.org/10.1039/d0fo02736g
59. Deng Y, Ma J, Weng X, et al. Kaempferol-3-O-glucuronide ameliorates non-alcoholic steatohepatitis in high-cholesterol-diet-induced larval zebrafish and HepG2 cell models via regulating oxidation stress. *Life* (*Basel*). 2021;11(5):445. https://doi.org/10.3390/life11050445
60. Ma C, Wang Z, Xia R, et al. Danthron ameliorates obesity and MAFLD through activating the interplay between PPARα/RXRα heterodimer and adiponectin receptor 2. *Biomed Pharmacother*. 2021;137:111344. https://doi.org/10.1016/j.biopha.2021.111344
61. Ye M, Tang Y, He J, et al. Alleviation of non-alcoholic fatty liver disease by Huazhi Fugan granules is associated with suppression of TLR4/NF-κB signaling pathway. *Clin Investig Arterioscler*. 2021;33(5):257–266. https://doi.org/10.1016/j.arteri.2020.12.007
62. Ying Y, Zhang H, Yu D, Zhang W, Zhou D, Liu S. Gegen Qinlian decoction ameliorates nonalcoholic fatty liver disease in rats via oxidative stress, inflammation, and the NLRP3 signal axis. *Evid Based Complement Alternat Med*. 2021;2021:6659445. https://doi.org/10.1155/2021/6659445
63. Wu SJ, Huang WC, Yu MC, et al. Tomatidine ameliorates obesity-induced nonalcoholic fatty liver disease in mice. *J Nutr Biochem*. 2021 May;91:108602. https://doi.org/10.1016/j.jnutbio.2021.108602
64. Wang S, Sheng F, Zou L, Xiao J, Li P. Hyperoside attenuates non-alcoholic fatty liver disease in rats via cholesterol metabolism and bile acid metabolism. *J Adv Res*. 2021;34:109–122. https://doi.org/10.1016/j.jare.2021.06.001
65. Chang GR, Lin WL, Lin TC, Liao HJ, Lu YW. The ameliorative effects of saikosaponin in thioacetamide-induced liver injury and non-alcoholic fatty liver disease in mice. *Int J Mol Sci*. 2021;22(21):11383. https://doi.org/10.3390/ijms222111383
66. Sui M, Jiang X, Sun H, et al. Berberine ameliorates hepatic insulin resistance by regulating microRNA-146b/SIRT1 pathway. *Diabetes Metab Syndr Obes*. 2021;14:2525–2537. https://doi.org/10.2147/DMSO.S313068
67. Gao X, Cao W. Curative effects of traditional Chinese medicine on liver fibrosis: a protocol for a systematic review and meta-analysis. *Medicine* (*Baltimore*). 2021;100(9):e24587. https://doi.org/10.1097/MD.0000000000024587
68. Ji D, Zhao Q, Qin Y, et al. Germacrone improves liver fibrosis by regulating the PI3K/AKT/mTOR signalling pathway. *Cell Biol Int*. 2021;45(9):1866–1875. https://doi.org/10.1002/cbin.11607
69. Xiao Z, Ji Q, Fu YD, et al. Amygdalin ameliorates liver fibrosis through inhibiting activation of TGF-β/Smad signaling [published online Nov 24, 2021]. *Chin J Integr Med*. 2021. https://doi.org/10.1007/s11655-021-3304-y
70. Wang H, Che J, Cui K, et al. Schisantherin A ameliorates liver fibrosis through TGF-β1mediated activation of TAK1/MAPK and NF-κB pathways in vitro and in vivo. *Phytomedicine*. 2021;88:153609. https://doi.org/10.1016/j.phymed.2021.153609
71. Lin L, Zhou M, Que R, et al. Saikosaponin-d protects against liver fibrosis by regulating the estrogen receptor-β/NLRP3 inflammasome pathway. *Biochem Cell Biol*. 2021;99(5):666–674. https://doi.org/10.1139/bcb-2020-0561
72. Ye QN, Zhao CQ, Ping J, Xu LM. Study on mechanism of salidroside against liver fibrosis by regulating CXCL16. *China J Chin Mater Med*. 2021;46(11):2865–2870. (Chinese) https://doi.org/10.19540/j.cnki.cjcmm.20201224.401
73. Yang L, Bi L, Jin L, et al. Geniposide ameliorates liver fibrosis through reducing oxidative stress and inflammatory respose, inhibiting apoptosis and modulating overall metabolism. *Front Pharmacol*. 2021;12:772635. https://doi.org/10.3389/fphar.2021.772635
74. Kang R, Tian W, Cao W, et al. Ligustroflavone ameliorates CCl_4-induced liver fibrosis through down-regulating the TGF-β/Smad signaling pathway. *Chin J Nat Med*. 2021;19(3): 170–180. https://doi.org/10.1016/S1875-5364(21)60018-3
75. Cui B, Yang Z, Wang S, et al. The protective role of protocatechuic acid against chemically induced liver fibrosis in vitro and in vivo. *Pharmazie*. 2021;76(5):232–238. https://doi.org/10.1691/ph.2021.0909

76. Chen C, Gu J, Wang J, et al. Physcion 8-O-β-glucopyranoside ameliorates liver fibrosis through inflammation inhibition by regulating SIRT3-mediated NF-κB P65 nuclear expression. *Int Immunopharmacol*. 2021;90:107206. https://doi.org/10.1016/j.intimp.2020.107206
77. Xu Y, Zhang D, Yang H, et al. Hepatoprotective effect of genistein against dimethylnitrosamine-induced liver fibrosis in rats by regulating macrophage functional properties and inhibiting the JAK2/STAT3/SOCS3 signaling pathway. *Front Biosci* (*Landmark Ed*). 2021;26(12):1572–1584. https://doi.org/10.52586/5050
78. Fu Y, Xiao Z, Tian X, et al. The novel Chinese medicine JY5 formula alleviates hepatic fibrosis by inhibiting the Notch signaling pathway. *Front Pharmacol*. 2021;12:671152. https://doi.org/10.3389/fphar.2021.671152
79. Zhao J, Miao J, Wei X, et al. Traditional Chinese medicine Ganshuang granules attenuate CCl_4-induced hepatic fibrosis by modulating gut microbiota. *Chem Biodivers*. 2021;18(11): e2100520. https://doi.org/10.1002/cbdv.202100520
80. Zhou J, Zhang X, Wan L, et al. Zi Qi decoction alleviates liver fibrosis by inhibiting the Toll-like receptor 4 (TLR4)-related nuclear factor kappa b (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. *Med Sci Monit*. 2021;27:e929438. https://doi.org/10.12659/MSM.929438
81. Yang T, Xu R, Huo J, et al. WWOX activation by toosendanin suppresses hepatocellular carcinoma metastasis through JAK2/Stat3 and Wnt/β-catenin signaling. *Cancer Lett*. 2021;513: 50–62. https://doi.org/10.1016/j.canlet.2021.05.010
82. Zhou Y, Liu X, Gao Y, et al. Paeoniflorin affects hepatocellular carcinoma progression by inhibiting Wnt/β-catenin pathway through downregulation of 5-HT1D. *Curr Pharm Biotechnol*. 2021;22(9):1246–1253. https://doi.org/10.2174/1389201021666201009153808
83. Li ZJ, Dai HQ, Huang XW, et al. Artesunate synergizes with sorafenib to induce ferroptosis in hepatocellular carcinoma. *Acta Pharmacol Sin*. 2021;42(2):301–310. https://doi.org/10.1038/s41401-020-0478-3
84. Rong W, Wan N, Zheng X, et al. Chrysin inhibits hepatocellular carcinoma progression through suppressing programmed death ligand 1 expression. *Phytomedicine*. 2022;95:153867. https://doi.org/10.1016/j.phymed.2021.153867
85. Zhang L, Chai Z, Kong S, et al. Nujiangexanthone A inhibits hepatocellular carcinoma metastasis via down regulation of cofilin 1. *Front Cell Dev Biol*. 2021;9:644716. https://doi.org/10.3389/fcell.2021.644716
86. Zhou XQ, Mao XM, Fan R, et al. Trilobolide-6-O-isobutyrate suppresses hepatocellular carcinoma tumorigenesis through inhibition of IL-6/STAT3 signaling pathway. *Phytother Res*. 2021;35(10):5741–5753. https://doi.org/10.1002/ptr.7233
87. Liu HY, Dong TX, Li ZZ, et al. Homoharringtonine inhibits the progression of hepatocellular carcinoma by suppressing the PI3K/AKT/GSK3β/Slug signaling pathway. *Neoplasma*. 2021;68(5):924–937. https://doi.org/10.4149/neo_2021_210113N57
88. Guo C, Hou X, Liu Y, et al. Novel Chinese *Angelicae Sinensis Radix* polysaccharide biomimetic nanomedicine to curcumin delivery for hepatocellular carcinoma treatment and immunomodulatory effect. *Phytomedicine*. 2021;80:153356. https://doi.org/10.1016/j.phymed.2020.153356
89. Li M, Shang H, Wang T, Yang SQ, Li L. Huanglian decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression. *World J Gastroenterol*. 2021;27(10): 939–958. https://doi.org/10.3748/wjg.v27.i10.939
90. Shen Y, Yang F, Peng H, et al. Anti-tumor effect of Yanggan Huayu granule by inducing AKT-mediated apoptosis in hepatocellular carcinoma. *J Ethnopharmacol*. 2022;282:114601. https://doi.org/10.1016/j.jep.2021.114601
91. Zhang F, Xiao X, Li Y, et al. Therapeutic opportunities of GPBAR1 in cholestatic diseases. *Front Pharmacol*. 2022;12: 805269. https://doi.org/10.3389/fphar.2021.805269
92. Xiang J, Yang G, Ma C, et al. Tectorigenin alleviates intrahepatic cholestasis by inhibiting hepatic inflammation and bile accumulation via activation of PPARγ. *Br J Pharmacol*. 2021;178(12):2443–2460. https://doi.org/10.1111/bph.15429
93. Ma C, Xiang J, Huang G, et al. Pterostilbene alleviates cholestasis by promoting SIRT1 activity in hepatocytes and macrophages. *Front Pharmacol*. 2021;12:785403. https://doi.org/10.3389/fphar.2021.785403
94. Wu P, Qiao L, Yu H, et al. Arbutin alleviates the liver injury of α-naphthylisothiocyanate-induced cholestasis through farnesoid X receptor activation. *Front Cell Dev Biol*. 2021;9:758632. https://doi.org/10.3389/fcell.2021.758632
95. Xue H, Fang S, Zheng M, et al. Da-Huang-Xiao-Shi decoction protects against3, 5-diethoxycarbonyl-1,4-dihydroxycholllidine-induced chronic cholestasis by upregulating bile acid metabolic enzymes and efflux transporters. *J Ethnopharmacol*. 2021;269: 113706. https://doi.org/10.1016/j.jep.2020.113706
96. Liu G, Zhao W, Bai J, Cui J, Liang H, Lu B. Formononetin protects against concanavalin-A-induced autoimmune hepatitis in mice through its anti-apoptotic and anti-inflammatory properties. *Biochem Cell Biol*. 2021;99(2):231–240. https://doi.org/10.1139/bcb-2020-0197
97. Fan Z, Li Y, Chen S, et al. Magnesium isoglycyrrhizinate ameliorates concanavalin A-induced liver injury by inhibiting autophagy. *Front Pharmacol*. 2022;12:794319. https://doi.org/10.3389/fphar.2021.794319
98. Long L, Li H, Deng G, et al. Impact of hepatic encephalopathy on clinical characteristics and adverse outcomes in prospective and multicenter cohorts of patients with acute-on-chronic liver diseases. *Front Med* (*Lausanne*). 2021;8:709884. https://doi.org/10.3389/fmed.2021.709884
99. Lu B, Wu C, Azami NLB, et al. Babao Dan improves neurocognitive function by inhibiting inflammation in clinical minimal hepatic encephalopathy. *Biomed Pharmacother*. 2021;135:111084. https://doi.org/10.1016/j.biopha.2020.111084
100. Huang J, Gong Z, Kong Y, et al. Electroacupuncture synergistically inhibits proinflammatory cytokine production and improves cognitive function in rats with cognitive impairment due to hepatic encephalopathy through p38MAPK/STAT3 and TLR4/NF-κB signaling pathways. *Evid Based Complement Alternat Med*. 2021;2021:7992688. https://doi.org/10.1155/2021/7992688
101. Ye Q, Jiang H, Lan Y, Wang M, Mao D. Therapeutic effects and associated mechanisms by which "Fuyang Jiedu Huayu" granules treat chronic liver failure in the rat. *Evid Based Complement Alternat Med*. 2021;2021:7634673. https://doi.org/10.1155/2021/7634673
102. Dai X, Feng J, Chen Y, et al. Traditional Chinese medicine in nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. *Chin Med*. 2021;16(1):68. https://doi.org/10.1186/s13020-021-00469-4
103. Fu K, Wang C, Ma C, Zhou H, Li Y. The potential application of Chinese medicine in liver diseases: a new opportunity. *Front Pharmacol*. 2021;12:771459. https://doi.org/10.3389/fphar.2021.771459