Pharmacological effects of Chinese medicine modulating NLRP3 inflammasomes in fatty liver treatment

Tingting Liu1,2,3,4†, Guang Xu2*, Longxin Liang1†, Xiaohe Xiao1, Yanling Zhao5* and Zhaofang Bai1,2*

1Senior Department of Hepatology, Fifth Medical Center of PLA General Hospital, Beijing, China, 2Military Institute of Chinese Materia, Fifth Medical Center of PLA General Hospital, Beijing, China, 3School of Traditional Chinese Medicine, Capital Medical University, Beijing, China, 4The Third Affiliated Hospital of Zunyi Medical University (The First People’s Hospital of Zunyi), Guizhou, China, 5Department of Pharmacy, The Fifth Medical Center of PLA General Hospital, Beijing, China

Inflammation is a key contributing factor in the pathogenesis of fatty liver diseases (FLD), such as nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver diseases (ALDs). The NLRP3 inflammasome is widely present in the hepatic parenchymal and non-parenchymal cells, which are assembled and activated by sensing intracellular and extracellular danger signals resulting in the matures of IL-1β/IL-18 and pyroptosis. Moreover, the aberrant activation of the NLRP3 inflammasome is considered the main factor to drives immune outbreaks in relation to hepatic injury, inflammation, steatosis, and fibrosis. Therefore, inhibition of NLRP3 inflammasome may be a promising therapeutic target for FLD. Currently, accumulating evidence has revealed that a number of traditional Chinese medicines (TCM) exert beneficial effects on liver injury via inhibiting the NLRP3 inflammasome activation. Here, we summarized the mechanism of NLRP3 inflammasomes in the progression of FLD, and TCM exerts beneficial effects on FLD via positive modulation of inflammation. We describe that TCM is a promising valuable resource for the prevention and treatment agents against FLD and has the potential to be developed into clinical drugs.

KEYWORDS
Chinese medicine, NLRP3 inflammasome, inhibitor, NAFLD, ALD, liver fibrosis

Introduction

Liver diseases have been a global health concern and ranked as one of the major causes of morbidity and mortality worldwide (Asrani et al., 2019). Among the various forms of liver disease, FLD has become the most common liver disease globally, which is associated with fibrosis and the risk of hepatocellular carcinoma and has been classified into NAFLD and ALD (The global, 2020). The vast majority of Europe and Asia encounter a huge burden of fatty liver pathologies, and about 25% of the European population is affected by NAFLD (Younossi et al., 2018). Moreover, approximately 300 million Chinese people...
suffer from liver disease. Notably, in contrast to the number of newly HBV-infected patients, the burden of NAFLD and ALD in China continued to grow, paralleling the increase in obesity (Wang et al., 2014; Pimpin et al., 2018; Younossi et al., 2018).

The liver is anatomically and physiologically connected to the gut, leading to the liver being constantly exposed to the gut-derived pathogen-associated molecular patterns (PAMPs), such as microbial and toxins, which trigger immune responses (Zhang et al., 2021a). In addition to PAMPs, hepatic inflammation is also activated by intracellular damage signals, which are released by damaged or dying hepatocytes (called damage-associated molecular patterns, DAMPs) (Kubes and Mehal, 2012). PAMPs and DAMPs can be recognized by pattern recognition receptors (PRRs) to induce PAMPs- and DAMPs-triggered immunity and test studies of PRRs include NOD-like receptors (NLR), Toll-like receptors (TLR), and AIM2-like receptors (AIM2) (Takeuchi and Akira, 2010). NLRP3, as the best characterized NLRs, is activated by PAMPs or DAMPs and promotes the expression of inflammatory cytokines to amplify the inflammatory response. The aberrant activation of NLRP3 inflammasome is considered the main driving force behind excessive immune outbreaks. Increasing studies have indicated that the aberration of the NLRP3 inflammasome is implicated in liver diseases, including drug-induced liver injury (DILI), hepatocellular carcinoma (HCC), cholestatic liver injury (CLI), and autoimmune hepatitis (AIH) (Neumann et al., 2018). For example, previous studies demonstrated that traditional Chinese medicines (TCMs), such as Epimedii Folium [Berberidaceae; Epimedium brevicornu Maxim.,], Psoralae Fructus [Leguminosae; Psoralea corylifolia L.], and Sophora flavescens [Leguminosae; Sophorae flavescentis Radix], as well as some chemical drugs carbamazepine, isoniazid, and nevirapine, promote NLRP3 inflammasome activation and result in liver injury (Wang et al., 2019a; Gao et al., 2021; Qin et al., 2021; and Lin et al., 2022). A clinical study showed that NLRP3 inflammasome activation exhibits a protective effect on the development of HCC, but other experimental data indicated that NLRP3 deficiency in HCC cells enhance surveillance of NK cells to delay the tumor development in the xenograft mice model (Wei et al., 2014; Lee et al., 2021). Some research studies showed a high level of NLRP3 expression in cholestatic liver injury via the S1P/S1PR2 pathway (Hou et al., 2021). Over-activation of the NLRP3 inflammasome has also been found in trichloroethene- and ConA-induced autoimmune hepatitis mice models, indicating that the inflammasome activation-dependent IL-1β and pyroptosis contributed to exacerbating the liver injury (Luan et al., 2018; Wang et al., 2019b). Emerging evidence revealed that NLRP3 inflammasome activation is a driver of the pathological process of FLD (including NAFLD and ALD), which contributes to hepatic steatosis, liver tissue damage, and necrotic cell death (Del Campo et al., 2018). In both NASH and ALD patients, the level of IL-1β was increased and contributed to the progression of the disease (Tilg et al., 1992; Henao-Mejia et al., 2012). In accordance with human NAFLD and ALD patients, the expressions of NLRP3 and IL-1β were significantly increased in NAFLD and ALD mouse models (Knorr et al., 2020). Hence, NLRP3 inflammasomes might be a novel target for the treatment of liver disease, especially in FLD.

Currently, there is still no availability of approved pharmacological agents approved for the management of ALD and lifestyle modification, such as weight loss and alcohol abstinence, is considered the best therapeutic strategy (Pessone et al., 2003; Ferro et al., 2020). Several market-available drugs have been evaluated in ALDs, such as vitamin E, metformin, and statins, but most of them only provide limited success (Sanyal et al., 2010; Ford et al., 2015; Tziomalos et al., 2015). Thus, there is an urgent need to identify a high efficacy and minimal side effects treatment for ALD. Traditional Chinese medicine (TCM) has a long history of complementary and therapy applications in many countries (Zhang et al., 2021b), and the efficacy and safety for many diseases have been widely verified via long-term empirical trials (Li et al., 2017; Yang et al., 2019). Recently, TCM has gained much attention as a potential application in the prevention and treatment of FLD due to the characteristic of multi-targets, multi-pathway, and less toxic side effects. ALDs are referred to as “Gan-Pi” (NAFLD) or “Jiu-Pi” (ALD), respectively, due to the different etiology in Chinese medicine, and “internal retention of phlegm and dampness”, “liver qi stagnation”, “blood stasis”, and “a deficiency of spleen or kidney” is considered as its pathogenesis (Zhu et al., 2021a; Dong et al., 2012; Zhang et al., 2022). Thus, the main principle of Chinese medicine in the treatment of ALD involves evacuating phlegm and dampness from the body, relieving qi stagnancy in the liver, removing blood stasis, and strengthening the function of the spleen and kidney (Dong et al., 2012; Zhang et al., 2022). According to the therapeutics in Chinese medicine, numerous Chinese herbal formulations have been proposed and used for FLD (Tables 1, 2).

Emerging immunological studies also show that NLRP3 inflammasomes play an important role in the development of FLD and might be a promising therapeutic target for the treatment of FLD. Moreover, a variety of Chinese herbal formulations, TCM extracts, and natural products exert a wide range of anti-inflammatory effects by inhibiting the activation of the NLRP3 inflammasome and showing a potent and effective effect in various FLD (Fan et al., 2020; Wang et al., 2022). In this review, we systematically summarized the role and mechanisms of NLRP3 inflammasome activation in FLD and how the TCM targets and regulates NLRP3 inflammasome to improve the development of FLD.
TABLE 1 Therapeutic effects of traditional Chinese medicine formulas on FLD.

| Chinese medicine formulas | Common composition | Model | Effect | Mechanisms | Ref |
|---------------------------|-------------------|-------|--------|------------|-----|
| Gegen Qinlian decoction   | Pueraria lobata (Willk.) Ohwi [Leguminosae; Pueraria Lobata Radix], Coptis chinensis Franch [Ranunculaceae, Coptidis Rhizoma], Scutellaria baicalensis Georgi [Lamiaceae; Scutellariae Radix], Glycyrrhiza | HFD fed rat model | Decrease serum triglyceride, cholesterol, total bile acid, low-density lipoprotein, free fatty acid, and LPS level | Inhibiting TLR4 signal pathways | Zhang et al. (2020) |
| Fuzi Lizhong decoction    | Codonopsis tangshen Oliv [Campanulaceae; Codonopsis Radix], Zingiber officinalis Rosc. [Zingiberaceae; Zingiberis Rhizoma], Aconitum carmichaelii Debx [Ranunculaceae, Aconiti Radix Cocta], Glycyrrhiza, Baizhu | HFD-fed rat model | Reduce serum total cholesterol, triglyceride, blood glucose, and fatty acid in the liver | Activating p53 and inhibiting PPARG signaling | Yang et al. (2020) |
| Lanzhang granules         | Gentianae Macrophylla Radix, Gentiana macrophylla Pall. | HFD-fed mice model | Improve lipid metabolism and inflammation, decrease serum ALT and AST levels | Regulation of the PPARa signaling pathway | Huang et al. (2022) |
| Yiqihuoxue formula        | Gentianae Macrophylla Radix, Gentiana macrophylla Pall. | HFD-fed rat model | Decrease serum ALT level and hepatic fatty deposition, upregulate serum gastrin and motilin | – | Chen et al. (2013) |
| Lingzhihuang decoction    | Poria, Cinnamomum cassia Preal [Lauraceae; Cinnamomi Ramulus], Baizhu, Glycyrrhiza | HFD-fed rat model | Alleviate hepatic steatosis and reduce 6-methyladenosine level | N6-methyladenosine modification-mediated suppressor of cytokine signaling | Dang et al. (2020) |
| Qianggan formula          | Artemisia capillaris Thunb [Asteraceae; Artemisiae Scopariae Herba], Isatis indigotica Fort. [Brassicaceae; Isatidis Radix], Angelica sinensis(Oliv.)Dels [Apiaceae; Angelicae Sinensis Radix], Paeonia lactiflora Pall. [Ranunculaceae, Paeoniae Radix Alba], Datisken, Curcuma Radix, Curcuma wenyujin Y.H.Chenet Ye [Zingiberaceae, Atragali Radix, Codonopsis Radix], Zexie, Polygonatum sibiricum Rad. [Liliaceae, Polygonatii Rhizoma], Dioscorea opposita Thumb [Dioscoreaceae, Dioscoreae Rhizoma, Crataegi Fructus], Medicated Leaven Massa Medicae Fermentata, Gentiana macrophylla Pall [Gentianaceae, Gentianae Macrophyllae Radix], Glycyrrhizae | MCD-fed mice model | Alleviated liver inflammation, TNF-α, IL-β expression, reduce serum ALT and AST levels | Regulate gut microbiota-mediated LCA production, promote TGR5 expression, and suppress the NF-κB activation | Li et al. (2020) |

The activation of NLRP3 inflammasomes and potential modulating factors

NLRP3 inflammasomes are well known as cytosolic multiprotein complexes consisting of the innate immune sensor protein NLRP3 (also called Cryopyrin), adaptor speck-like protein (ASC), and the caspase-1 protease (Deng et al., 2019). Some studies indicated that NLRP3 may act as a sensor of the homeostatic intracellular process that is activated by sensing the intracellular and extracellular PAMPs and DAMPs (Masters et al., 2010). Typically, the NLRP3 inflammasome activation requires a two-step process, including priming and activating (Figure 1). First, the priming step is usually induced by lipopolysaccharide (LPS), activating the transcription factor
nuclear factor-kappa B (NF-κB) to upregulate the transcription of inflammasome proteins and pro-cytokines (pro-IL-1β, pro-IL-18). Second, the activating step is provided by a diverse group of DAMPs and PAMPs, such as ATP, cholesterol, reactive oxygen species (ROS), etc., that assemble and activate the NLRP3 inflammasome through three main pathways. 1) Extracellular ATP binds to the ionotropic P2X purinoceptor7 (P2X7) and activates the NLRP3 inflammasome by inducing intracellular K⁺ efflux (Carta et al., 2006). Moreover, the persistently activated P2X7 recruit membrane pore protein pannexin-1 and presumably formed, the "P2X7-PANX1 pore complex", which allows a variety of PAMPs and DAMPs into the cytosol to trigger NLRP3 inflammasome activation (Kanneganti et al., 2007). 2) The endocytosis of crystals or large particles (amyloid, silica, cholesterol, etc.) induced lysosomal damage, leading to their components and lysosomal proteases release to induce NLRP3 inflammasome activation (Kannel et al., 2008; Hornung et al., 2008; Broz and Dixit, 2016). 3) The increase of ROS leads to thioredoxin-interacting protein (TXNIP) translocating from the nucleus to the cytoplasm and bound to thioredoxin to associated with NLRP3 inflammasome activation (Brocker et al., 2020). Subsequently, the activated NLRP3/ASC/ pro-caspase-1 complex converts pro-caspase-1 to caspase-1, which in turn processes the mature pro-IL-1β/pro-IL-18 into their secretory bio-active (IL-1β/IL-18) forms, triggering the inflammatory cascade and gasdermin D (GSDMD) cleavage (Basiorka et al., 2016). In addition to the above three main pathways, numerous NLRP3-interacting proteins, including mitosis A-related kinase-7 (NEK7), heat shock protein 90 (HSP90), etc., have been proved to promote the activation of NLRP3 inflammasomes (Duan et al., 2020).

Historically, inflammasomes are central to regulating liver diseases, which has been attributed to their ability to induce hepatic inflammation by up-regulating the expression of IL-1β/IL-18. Increasing clinical and experimental studies have demonstrated that inflammasome activation-dependent IL-1β is a major cause and contributes to liver disease progression (Iracheta-Vellve et al., 2017). The secreted active IL-1β synergistic action with TLR signaling amplifies inflammation by increasing the expression of pro-IL-1β, TNF, CCL2, etc. (Granowitz et al., 1992; Mandrekar et al., 2011). Moreover, IL-1β promotes hepatic stellate cells (HSCs) activation, resulting in liver fibrosis, as well as enhances the accumulation of triglyceride and hepatocyte injury contributing to liver steatosis (Miura et al., 2010; Petrasek et al., 2011). Compared to IL-1β, IL-18 aggravates NASH severity via altering the gut microbiota, and it has been proved in the MCD diet-induced NASH model that IL-18-deficient mice progressed to severe NASH more than the control group (Henao-Mejia et al., 2012). However, the role of IL-1β/IL-18 in NAFLD and ALD remains to be elucidated, and the underlying mechanisms require deep investigation.
The activation of the NLRP3 inflammasome requires two steps: first, DAMPs, PAMPs, or cytokines bind to their receptors, leading to the NF-κB signaling pathway activation, resulting in the increased expression of pro-IL-1β/IL-18 and inflammasome components. Second, several DAMPs and PAMPs induce the activation of the NLRP3 inflammasome to trigger caspase-1 cleavage and IL-1β/IL-18 mature. Subsequently, activated caspase-1 cleaves GSDMD to GSDMD-N, resulting in pyroptosis.

**TCM for the treatment of NAFLD by inhibiting the NLRP3 inflammasome**

NAFLD is the most frequent type of FLD, affecting more than 20% of people worldwide, and is highly correlated with obesity and metabolic syndrome (Lee et al., 2020). The clinical spectrum of NAFLD is spanned from noninflammatory isolated hepatic steatosis, NASH, progressive to cirrhosis, or even carcinoma (HCC) (Arab et al., 2018). NASH is a severe liver condition that is characterized by hepatocellular damage, steatosis, inflammation, and fibrogenesis. Approximately 10–30% of patients with NAFLD will develop NASH (Liang et al., 2018). A “two-hit” hypothesis that explains the progression of NAFLD into NASH. The “first hit” involves an abnormal accumulation of lipid and insulin resistance that leads to hepatic steatosis, thereby resulting in the liver being susceptible to “second hits” including dysfunction of mitochondria, endotoxins, inflammation, and oxidative stress. Emerging evidence has indicated that NLRP3 inflammasome activation is implicated in metabolic syndrome, obesity, and NAFLD (Szabo and Csak, 2012; Lee et al., 2013; Esser et al., 2014). Recently, increasing clinical and experimental studies have shown the expression of NLRP3 inflammasome components (NLRP3, caspase-1, and ASC) was remarkably increased in the patients with NAFLD and in the mice model (Wree et al., 2014; Mitsuysoshi et al., 2017; Gaul et al., 2021). Moreover, both NLRP3 inflammasome components, deficient or treated with NLRP3 inhibitors, attenuated the inflammation, liver fibrosis, and liver cell death in a mouse model, which further demonstrated the role of the NLRP3 inflammasome in NAFLD (Dixon et al., 2013; Li et al., 2022). In animal models, feeding rodents a diet deficient in methionine and choline (MCD) is a classic method of inducing NASH, as well as a prolonged high-fat diet (HFD) and high-fat/high-cholesterol/high-sugar diet (HF-HC-HSD). It is noteworthy that the short period of HFD or HF-HC-HSD feeding causes hepatic steatosis but not NASH (Ganz et al., 2015; Farrell et al., 2019).

Most types of TCMs, including TCM formulas, extracts, and its natural products, have been used in treating NAFLD and exhibit a promising treatment efficacy via modulating a variety of risk signals in the process of NAFLD, such as oxidized lipids, DAMPs, and ROS, resulting result in NLRP3 expression in liver tissue through TLR4 (Farrell et al., 2018; Wang et al., 2020; Zhang et al., 2020). Many of them showed a potent effect in modulating NLRP3 inflammasome activation by regulating inflammasome activation-associated signaling pathways, such as the release of ROS, LPS, NF-κB, toll-like, etc. Dansheng Zexie decoction is the water extract of three Chinese medicines, including Salvia miltiorrhiza Bunge (Danshen, 15 g), Alisma miltiorrhiza radix, and rhizoma, Alisma plantago-aquatica Linn. (Zexie, 30 g), and Atractylodes macrocephala Koidz. (Baizhu, 12 g). Among them, Dansheng Zexie decoction has been frequently used for the prevention and treatment of chronic diseases (NAFLD and gastroenteropathy), significantly improving lipid peroxidation, inflammation, and liver fibrosis (Yang et al., 2014). The CSS contributes to the reducing serum LPS level, NLRP3 expression, liver steatosis, and reconstruction of the intestinal microflora in the HFD-fed rat model, all processes associated with the NLRP3 inflammasome pathway, suggesting that the inhibition...
of NLRP3 inflammasome activation is responsible for the treatment of NAFLD with CSS (Liang et al., 2018b).

*Antrodia cinnamomea* (AC) [Polyporaceae; *Antrodia camphorata*], a fungus of the Fomitopsidaceae family, has been used for treating many kinds of diseases and showed an effect in reducing hepatic triglycerides and total cholesterol concentrations in the HFD hamster model. Recent studies demonstrated that the AC ethanol extract attenuated steatohepatitis, oxidative stress, hepatic inflammation, ameliorating the MCD-diet-induced NAFLD by inhibiting NLRP3 inflammasome activation (Yen et al., 2020). Honey, a natural substance produced by bees from nectar, is a classical medicinal and edible TCM that has been investigated and used for various diseases, such as chemical-induced liver injury, hepatic cancer, and diabetes (Erejuwa et al., 2010; El-kott et al., 2012; Al-Yahya et al., 2013). In recent studies, honey has been used for treating NAFLD and showed a potent effect in improving hepatic histology, lipid metabolism, oxidative stress, and hepatic inflammation via inhibiting the TXNIP-NLRP3 pathway in the HFD-fed rat model (Xiao et al., 2016). *Rheum palmatum L.* (RP) [Polygonaecae; Rhei Radix Et Rhizoma] is one of the most used TCM for “pursing fire and detoxification” and “promoting blood circulation for removing blood stasis” in clinical Chinese medicine, which is frequently prescribed for treating a set of metabolic disorders, and the RP aqueous extract has been reported to ameliorate NAFLD (Yang et al., 2016). Recent studies demonstrated that the RP aqueous extract improved the MCD diet-induced serum inflammation and liver function by inhibiting the activation of NLRP3 inflammasome in vivo (Wu et al., 2022).

In addition, numerous natural products isolated from TCMs have been shown to address the treatment potentials of NAFLD through modulating the NLRP3 inflammasome. Increasing studies showed that many natural products of GL exhibit a potent effect in the treatment of NAFLD. *Glycyrrhiza uralensis Fisch.* (GL) is one of the most popular TCM in clinical Chinese medicine shows a wide range of biological activities and common therapies for multisystem inflammatory diseases, such as NAFLD (El-Saber Batiha et al., 2020). A randomized double-blind clinical trial of treating NAFLD demonstrated that licorice, the powder from the root of GL, supplementation contributes to a reduction of ALT levels and liver steatosis in patients with lifestyle modification, suggesting that licorice supplementation can improve the effectiveness of lifestyle modification alone in treating NAFLD (Rostamizadeh et al., 2022). Our group’s previous studies showed that licochalcone B (flavonoids from GL) inhibits NLRP3 inflammasome activation by preventing NEK7 from binding to NLRP3, and echinatin (flavonoids from GL) showed a negative effect on NLRP3 inflammasome activation by binding to HSP90. Furthermore, both licochalcone B and echinatin attenuate the MCD-induced increase of alanine transaminase (ALT) and aminotransferase (AST), liver inflammation changes, hepatic steatosis, and fibrosis (Xu et al., 2021; Li et al., 2022). In addition, another study also found that both glycyrrhizin and glycyrhetinic acid (terpenoids from GL) alleviated the degree of inflammation infiltration and lipid disruption in MCD-diet mice (Yan et al., 2018a). Baicalin (a flavonoid glycoside from *Scutellaria baicalensis Georgi* [Lamiaceae; Scutellariae Radix]) significantly reduced NLRP3, gasdermin D (GSDMD), IL-1β expression, and protected hepatocytes from free fatty acids-induced morphological damage and death, protecting hepatocytes from apoptosis by blocking NLRP3-GSDMD signaling in vitro (Shi et al., 2020a). Berberine is an isoquinoline alkaloid isolated from numerous herbal plants, which significantly ameliorated lipid accumulation, reducing TNF-α expression and phosphorylation of NF-κB, and inhibiting NLRP3 inflammasome activation by modulating the ROS/TXNIP axis in MCD-diet mice model (Mai et al., 2020). Emodin, rhein, diacerein, aloe-emodin, and 1,8-dihydroxyanthraquinone are free anthraquinones from *Rheum palmatum L.*, and all of them remarkably decreased serum ALT, AST, IL-1β, and TNF-α levels, improved hepatic inflammation, and fibrosis by blocking the activation of the NLRP3 inflammasome and the underlying mechanism of this role is related to inhibited ASC oligomerization.

**TCM for the treatment of ALD by inhibiting the NLRP3 inflammasome**

A major cause of ALD is due to the intake of excessive alcohol and is similar to NAFLD in pathology, ranging from hepatic steatohepatitis to fibrosis and cirrhosis (Silva et al., 2017). The early stage of ALD can be reversible with limited alcohol intake, but the advanced stages (including cirrhosis and severe alcoholic hepatitis) are irreversible, with fatal outcomes mediated by liver failure (Szabo et al., 2006). Activation of NLRP3 inflammation plays an important role in the progression of ALD, and the increased IL-1β and neutrophilia are characteristic features of sterile inflammation. The expression of IL-1β is significantly increased in patients with ALD, which is more than 10 times higher than in healthy controls (McClain et al., 1986). Moreover, the level of NLRP3 inflammasome components and IL-1β are increased in mice fed with excess ethanol (Petrasek et al., 2012). Similarly, caspase-1 or ASC deficient and IL-1 receptor knockout mice showed decreased ethanol-induced hepatic injury and steatosis (Petrasek et al., 2012). Moreover, liver macrophages (Kupffer cells) were important in mediating inflammasome activation in the progression of ALD (Adachi et al., 1994). The activation of the inflammasome is triggered by a variety of potential molecules in ALD, including DAMPs and PAMPs. Alcohol-induced intestinal barrier, leading to gut permeability, increased along with the leakage of gut microbiota product lipopolysaccharide (LPS) (DeSantis et al., 2013). Subsequently, the LPS binds to the TLR4 on Kupffer cells, which acts as the
priming signal to induce the inflammasome component’s gene expression, to activate the NLRP3 inflammasome (Ganz et al., 2011). Additionally, alcohol-induced hepatocyte damage results in the release of DAMPs (ATP and uric acid) and mediated inflammasome activation (Tilg et al., 2016). It was verified by clinical and experimental studies that the increase in ATP and uric acid have been found in alcohol-fed healthy humans (Petrasek et al., 2015) and mice that were fed the ethanol diet (Iracheta-Vellve et al., 2015). Both P2X7-deficient and uric acid-inhibited mice lack inflammasome activation in alcohol-fed groups (Petrasek et al., 2015).

Many kinds of TCMs that play an important role in the development of ALD and have been used for the treatment of ALD. Lycium barbarum L. (LB) [Solanaceae; Lycii Fructus], a traditional TCM has a wide range of pharmacological effects, such as anti-inflammation, antioxidation, and hepatoprotective, and is usually used for “nourishing the liver” in clinical Chinese medicine (Chang and So, 2008; Tang et al., 2017). Recently, the LB polysaccharides (LBPs), the liquid fraction extracted from LB, showed an effect on ameliorating the progression of ALD, in vitro experiments confirm that LB could reduce ethanol-induced oxidative stress, apoptosis, and the underlying mechanism of this role is proved by inhibiting NLRP3 inflammasome activation (Cheng and Kong, 2011; Xiao et al., 2014a). Moreover, zeaxanthin dipalmitate (ZD), one of the carotenoids of LB, showed an inhibiting effect on the NLRP3 inflammasome via modulating P2X7 and adipoR1, and drastically reduced inflammation infiltration and accumulation of fatty droplets in the ALD model rat (Gao et al., 2019).

In addition, many other natural products from TCM are also able to improve the development of ALD, such as gentiopicroside and active terpenoids of Gentiana Manchuria Kitag. [Gentianaceae; Gentianae Radix Et Rhizoma] regulated P2X7-NLRP3 to decrease the accumulation of aminotransferases and triglycerides in serum and reduced liver lipogenesis (Li et al., 2018).

Quercetin, a flavonoid from many TCMs, and ginsenoside Rg1, a natural terpenoid derived from PG, both showed a marked decrease effect on serum AST and ALT production, ameliorating the liver histology by inhibiting the activation of NLRP3 inflammasome via blocking oxidant stress in alcohol-fed mice and rats (Liu et al., 2018; Yang et al., 2021).

**TCM for the treatment of liver fibrosis by inhibiting the NLRP3 inflammasome**

Liver fibrosis is a result of chronic liver inflammation that is majorly regulated by the inflammasome, and the advanced form of fibrosis is responsible for liver failure (Bataller and Brenner, 2005). Numerous studies have indicated that the activation of the NLRP3 inflammasome is a critical contributor to the development of liver fibrosis. The inflammasome activator (uric acid crystals) increase the expression of transforming growth factor (TGF)-β1 to
TABLE 2 Therapeutic effects of Botanical drugs and natural products on FLD.

| Type       | Botanical drug/natural product | Model          | Effect                                                                 | Mechanisms                                                                 | Ref                  |
|------------|--------------------------------|----------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|----------------------|
| Extracts   | Powder of Platycodon grandiflorus [Campanulaceae; Platycodonis Radix] | HFD-fed mice model | Improve hyperlipidemia, liver steatosis, oxidative stress, inflammation, and insulin resistance | Activate the PI3K/Akt/GSK3 pathway | Ke et al. (2020)     |
|            | Ethanol extracts from Coix lacryma-jobi L. [Poaceae; Coicis Semen] | HFD-fed mice model | Alleviated liver steatosis and inflammation                            | Inhibit liver lipogenesis and induce fatty acid β-oxidation               | Chiang et al. (2020) |
|            | Water extracts from Coix lacryma-jobi L. | HFD-fed mice model | Alleviate lipid accumulation, intestinal barrier damage, liver injury, and hepatic inflammation | Regulate gut microbiota                                                   | Luo et al. (2021)    |
|            | Ethanol extracts from Cassia obtusifolia L. [Leguminosae; Cassiae Semen] | HFD-fed mice model | Decrease cyclooxygenase-2, TNF-α, and IL-6 expression, improve hepatocyte apoptosis | Anti-oxidative                                                        | Liang et al. (2021)  |
|            | Ethanol extracts from Morus alba L. [Moraceae; Mulberry leaves] | Alcohol-fed mice model | Decrease serum ALT, AST, ALP, triglyceride levels, hepatic NO, MDA, TNF-α, and IL-6 level | Regulate lipid metabolism                                                   | Qiao et al. (2019)   |
|            | Ethanol extracts from Portulaca oleracea L. [Portulacaceae; Portulaceae Herba] | Alcohol-fed rat model | Decrease serum ALT, AST, ALP, triglyceride levels, hepatic NO, MDA, TNF-α, and IL-6 level | Downregulate LXRs/SREBP-1c/ FAS/ASC and SREBP-2/HMGCR signaling pathways      | Wang et al. (2016)   |
| Polysaccharide of Schisandra chinensis (Turcz.)Baill. [Magnoliaceae; Schisandræ Chinensis Fructus] | HFD-fed mice model | Decrease serum triglycerides, total, alleviate hepatocyte fatty degeneration and necrosis | Decrease de novo lipogenesis, promote export of lipids, improve fatty acids oxidation | Xu et al. (2020)      |
| Patchouli Oil [Lamiaceae; Pogostemon cablin(Blanche) Benth. ] | HFD-fed rat model | Decrease lipid profiles and serum enzymes                                | Regulate lipid metabolism                                                   | Qiu et al. (2018)     |
| Flavonoids | Isoquercetin                    | HFD-fed rat model | Improve liver lipid accumulation, inflammation, and oxidative stress     | Activate the AMPK pathway and suppress the TGF-β signal                    | Qin et al. (2018)     |
| Adenosines | Cordycepin                     | HFD-fed mice model | Decrease serum aminotransferases, hepatic triglyceride, inflammation, and fibrosis | Activate the AMPK signaling pathway                                       | Lan et al. (2021)    |
| Phenols    | Curcumin                       | High-fat- and high-fructose- fed mice model | Improve hepatic steatosis and serum biochemical parameters | Regulate the Nrf2/FXR/LXRα pathway                                       | Yan et al. (2018b)   |
|            |                                | Alcohol-fed mice model | Improve hepatocyte necroptosis                                           | Regulate4 Nrf2/p53 pathway                                                | Lu et al. (2016)     |
| Phenols    | Gastrodin                      | Alcohol-fed mice model | Reduce serum ALT, AST, and MDA levels, hepatic glutathione peroxidase, and catalase expression | Enhance Nrf2 translocation to the nucleus                                 | Li et al. (2019)     |

activate the hepatic stellate cells (HSCs), triggering collagen production and deposition in humans and mouse, but does not occur in ASC-deficient situation (Watanabe et al., 2009). Kupffer cell activation-dependent IL-1 also is an indirect factor in the progression of fibrosis, which activates HSC by binding to IL-1β receptors (Weiskirchen and Tacke, 2014). Furthermore, some experimental studies showed that NLRP3 or ASC deficiency protects mice from carbon tetrachloride (CCL₄)-induced increase of hepatic TFG-β1 and collagen-1a1 expression. NLRP3 knock-out reduced liver fibrosis and inflammation in NASH model mice (Gaul et al., 2021).

25-0CH₃-PDD (PDD), one of the ginsenosides derived from PG, showed an activation effect on LXRs to inhibit P2X7-mediated NLRP3 inflammasome activation, decreasing serum ALT/AST expression and ameliorating liver injury and fibrosis in thioacetamide (TAA)-induced mouse model (Han et al., 2018). The liver X receptors (LXRs) are considered a critical regulator of energy metabolism, which had been reported to downregulate inflammatory gene expression, including il-1β, il-6, P2X7, etc., inhibiting inflammation (Zhu et al., 2012). Recently, a study showed that urso acid, a natural terpenoid isolated from a variety of herbal medicine, decreased collagen deposition and fibrosis-related factors expression and inhibited the level of NADPH oxidase 4 (NOX4) and NLRP3 in the CCL₄-induced liver fibrosis model. NOX4 activates liver fibrosis via regulating ROS to trigger apoptosis and HSC activation (Crosas-Molist and Fabregat, 2015). NLRP3 and NOX4 deficiency ameliorates the progression of ALD (Nie et al., 2021). In addition, alpinetin, a flavonoid isolated from Alpinia katsumadai [Zingiberaceae; Alpiniae Katsumadai Semen], also affects ameliorated liver injury and fibrosis via inhibiting NLRP3 inflammasome activation (Zhu et al., 2021b).
TABLE 3 Traditional Chinese medicine formulas for the treatment of FLD by inhibiting NLRP3 inflammasome activation.

| Chinese medicine formulas | Common composition | Model | Effect | Mechanisms | Ref |
|--------------------------|-------------------|-------|--------|------------|-----|
| Dansheng Zexie decoction | Baizhu, Zexie, Danshe | HFD-fed rat model | Decrease lipid accumulation, alleviate hepatic steatosis and mitotic stress | ROS/NLRP3/IL-1β | Biao et al. (2022) |
| Shenling Baizhu powder | Dolichas lablab, Poria, Glycyrrhiza, Platycodononis Radix, Nelumbinis Semen, PG, Anomur Fructus, Dioscoreae Rhizoma, Cocis Semen, Baizhu | HFD-fed rat model | Reduce body weight, serum free fatty acid, and ameliorate liver microcirculation and ultrastructural abnormalities | TLR4/NLRP3 | Pan et al. (2021) |
| Chaahu-Shugan San decoction | Citri Reticulatae Pericarpium, Bupleuri Radix, Chungtungong Rhizoma, Cypers Rhizoma, Aurantii Fructus, Paeniae Radix Alba, Glycyrrhiza (6:6:5:5:5:5) | HFD-fed rat model | Reduce serum LPS level, liver steatosis, and reconstruct the intestinal microflora | -- | Yang et al. (2014) |
| Jinlida granules | PG, Polygonti Rhizoma, Atractylodes lancea(Thunb.)DC [Asteraceae, Atractylodes Rhizoma], Sophora Flavescentis Ait. [Leguminosae, Sophorae Flavescentis Radix], Ophiopogon japonicus (L.)Ker-Gawl. [Lilaceae, Ophiopogoni Radix], Rehmannia glutinosa Liboch [Scrophulariaceae, Rehmanniae Radix], Polygonum multiflorum Thunb, [Polygonaceae, Polygoni Multiflori Radix], Cornus officinalis Sieb. et Zucc. [Cornaceae, Corni Fructus], Porta, Eupatorium fortunei Turcz. [Asteraceae, Eupatorii Herba], Coptis chinensis Franch. [Ranunculaceae, Coptidis Rhizoma], Ophiopogon japonicus, Anemarrhena asphodeloides Bge. [Lilaceae, Anemarrhenae Rhizoma], Epimedi Foliu, Danshen, Lycii Fructus, Puerariae thomsonii Benth [Leguminosae, Puerariae Thomsonii Radix], Lithi chinensis Sonn. [Sapindaceae, Litchi semen] (10:12:6:5:12:5:9:8:12:8:5:5:5:8:8:12:12) | HFD-fed mice model | Alleviate insulin sensitivity and glucose tolerance, and suppress mRNA expression of caspase-1, IL-1β, and IL-18 | Anti-pyroptosis | Hao et al. (2022) |

Discussion

NLRP3 inflammasomes play a pivotal role in FLD, especially in the progression of chronic types, including NAFLD, ALD, and liver fibrosis (Figure 2). However, the current knowledge of the mechanism of NLRP3 inflammasome activation is still very limited, and there is a lack of efficient clinical drugs for targeting NLRP3 inflammasome. Currently, therapeutic strategies are aimed at inhibiting the NLRP3 inflammasome signaling pathway by using NLRP3, IL-1β, TNF-α, and caspase inhibitors. MCC950 is well known as an NLRP3-specific inhibitor, showing a promising therapeutic effect in a variety of NLRP3-dependent immunopathological mouse models, including colitis, steatohepatitis, etc., but it was withdrawn from phase II clinical trial for the treatment of rheumatoid arthritis due to hepatotoxicity (Mangan et al., 2018). In addition, antibodies or antagonists (canakinumab) are used as inhibitors for IL-1β, which have been evaluated in humans (Kuemmerle-Deschner et al., 2011); however, multiple pro-inflammatory cytokines are induced by NLRP3 inflammasome activation and the treatment strategies to block IL-1β still need further study. Pentoxifylline has been known as a selective inhibitor of TNF-α and has been used in treating patients with severe alcoholic hepatitis in a randomized study, but it did not improve outcomes (Thursz et al., 2015). GS-9450 is an effective caspase inhibitor for caspases 1, 8, and 9 and has been explored for NASH in a randomized, double-blind, placebo-controlled study, which demonstrated the potent effect in decreasing ALT levels safely and with tolerance. However, episodes of GS-9450-induced DILI occurred in a 6-month study in hepatitis C subjects, and the safety and efficacy of long-term caspase inhibitor in NASH still need to be further investigated (Ratziu et al., 2012).

TCM has been extensively applied for the prevention and treatment of various liver diseases, particularly FLD. Many Chinese herbal formulations, TCM extracts, and natural products exhibit beneficial effects on the progression of FLD via modulating the NLRP3 inflammasome pathway (Table 3, 4). Carnosol is one of the phenols isolated from Rosmarinus officinalis [Lamiaceae; Rosmarinus officinalis L.]; cryptotanshinone is a quinones components in Salvia miltiorrhiza Bunge and serves as therapeutics against NLRP3-drive disease, including LPS-induced mortality and MCD-fed induced NASH mouse model via inhibiting the activation of NLRP3 inflammasomes (Shi et al., 2020b; Liu et al., 2021). Therefore, TCM has shown promising therapeutic anti-inflammatory, antioxidant, and anti-fibrosis t that might take beneficial effects on curtailing the progression of ALD.
### Table 4: Botanical drugs and natural products for the treatment of FLD by inhibiting NLRP3 inflammasome activation.

| Type            | Botanical drug/natural product | Model                        | Effect                                                                 | Targeted pathways                                                                 | Ref                        |
|-----------------|-------------------------------|------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------|
| Extracts        | Ethanol extracts from *Antrodia cinnamomea* | MCD-fed rat model | Attenuate steatohepatitis, oxidative stress, and hepatic inflammation | --                                                                                 | Yen et al. (2020)          |
|                 | Water extracts from *Rheum palmatum L* | MCD-fed mouse model | Improve serum inflammation and liver function                           | NLRP3--ASC                                                                        | Wu et al. (2022)           |
|                 | *Lycium barbarum* Polysaccharide | MCD-fed mouse model | Decrease serum ALT and AST levels, hepatic oxidative stress, fibrosis, inflammation, and apoptosis | NF-KB/NLRP3                                                                      | Xiao et al. (2018)         |
|                 | Ethanol-induced hepatocyte BRL-3A cells | MCD-fed mice model | Improve cellular apoptosis, inflammation, and oxidative stress         | TXNIP-NLRP3                                                                      | Xiao et al. (2014a)        |
| Flavonoids      | Licochalcone B                 | MCD-fed mice model          | Decrease ALT and AST levels, liver inflammation, steatosis, and fibrosis | NLRP3-NEK7                                                                        | Li et al. (2022)           |
|                 | Echinatin                     | MCD-fed mice model          | Decrease ALT and AST levels, liver inflammation, steatosis, and fibrosis | NLRP3-HSP90                                                                       | Xu et al. (2021)           |
|                 | Quercetin                     | Alcohol-fed mice model      | Improve hepatic inflammation, reduce IL-1β, IL-6 expression and ROS release, and inhibit NF-κB activation | Heme oxygenase-1                                                                | Liu et al. (2018)          |
|                 | Silybin                        | HFD-fed mouse model         | Reduce thioredoxin-interacting protein and IL-1β expression, caspase-1 cleavage | NAD^+/SIRT                                                                       | Zhang et al. (2018)        |
|                 | Alpinetin                      | CCL4-induced mouse model    | Suppress liver inflammation and oxidative stress, decrease MDA level    | NLRP3, NF-κB; medium anti-oxidative stress                                         | Zha et al. (2021b)         |
|                 | Baicalin                       | Free fatty acid-induced HepG2 | Ameliorated morphological damage and death                             | NLRP3-GSDMD                                                                       | Shi et al. (2020a)         |
| Quinones        | Emodin                         | MCD-fed mouse model         | Improve serum ALT, AST, IL-1β, and TNF-α levels, hepatic inflammation, and fibrosis | ASC oligomerization                                                              | Wu et al. (2022)           |
|                 | Rhein                          | MCD-fed mouse model         | Improve serum ALT, AST, IL-1β, and TNF-α levels, hepatic inflammation, and fibrosis | ASC oligomerization                                                              | Wu et al. (2022)           |
|                 | Diacerein                      | MCD-fed mouse model         | Improve serum ALT, AST, IL-1β, and TNF-α levels, hepatic inflammation, and fibrosis | ASC oligomerization                                                              | Wu et al. (2022)           |
|                 | Aloe-emodin                    | MCD-fed mouse model         | Improve serum ALT, AST, IL-1β, and TNF-α levels, hepatic inflammation, and fibrosis | ASC oligomerization                                                              | Wu et al. (2022)           |
|                 | Cryptotanshione                | MCD-fed mouse model         | Decrease ALT and AST levels, improve hepatic inflammation, fat vacuoles, and fibrosis | Ca^2+ signaling                                                                   | Liu et al. (2021)          |
|                 | 1,8-dihydroxyanthraquinone     | MCD-fed mouse model         | Improve serum ALT, AST, IL-1β, and TNF-α levels, hepatic inflammation, and fibrosis | ASC oligomerization                                                              | Wu et al. (2022)           |
| Alkaloids       | Berberine                      | MCD-fed mouse model         | Reduce mortality and ALT, TNF-α expression and phosphorylation of NF-κB | P2X7                                                                              | Wang et al. (2021)         |
| Terpenoids      | Zeaxanthin Dipalmate           | LD-fed mice model           | Improve hepatocyte autophagy, liver inflammation                        | P2X7 and adipoiR1                                                                 | Xiao et al. (2014b)        |
|                 | Gardenoside                    | HFD-fed mouse model         | Improve ROS release, pyroptosis, and apoptosis                          | CTCF/DPP4                                                                        | Shen et al. (2021)         |
|                 | Gentioticcyoside               | LD-fed mouse model          | Decrease serum aminotransferases and triglyceride accumulation           | P2x7R-NLRP3                                                                       | Li et al. (2018)           |
|                 | Glycyrrhizin                   | MCD-fed mouse model         | Alleviate serum bile acids accumulation, hepatic steatosis, inflammation, and fibrosis | FXR                                                                               | Yan et al. (2018a)         |
|                 | Ginsenoside RgI                | HFD-fed mouse model         | Reduce liver weight triglyceride, liver free fatty acids, MDA levels, serum ALT, AST, total bilirubin level, improve hepatic steatosis, hepatocellular apoptosis, mitochondria damage | --                                                                                | Xu et al. (2018)           |
|                 | Alcohol-fed mouse model        | HFD-fed mouse model         | Improve glucose and insulin tolerance, decrease inflammation and lipid accumulation | SREBP-1C, MARCK                                                                  | Song et al. (2018)         |
|                 | Ursolic acid                   | ETOH-fed mouse model        | Reduce lipogenesis and promote lipid oxidation                           | HMGBl-TLR4                                                                        | Shang et al. (2022)        |
|                 | Carnosol                       | MCD-fed mouse model         | Decrease serum aminotransferases, hepatic triglyceride, inflammation, and fibrosis | NLRP3-HSP90                                                                       | Shi et al. (2020b)         |
|                 | Carnosic acid                  | HFD-fed mouse model         | Improve glucose and insulin tolerance, decrease inflammation and lipid accumulation | P3K/AKT, NLRP3/ NF-KB                                                           | Song et al. (2018)         |
|                 | 25-0CH3-PDD                    | TAA-induced mice model      | Improve serum ALT, AST, hepatic transcripts of pro-fibrogenic markers, hepatocyte apoptosis | LXRs-P2X7R                                                                        | Han et al. (2018)          |
In this review, we summarized and discussed recent research on Chinese herbal formulations, TCM extracts, and natural products that improve the status of ALD via inhibiting the NLRP3 inflammasome. Most of them, such as Glycyrrhiza, and Salvia miltiorrhiza Bunge, are commonly used in clinical practice, and their formulations and natural products can achieve an anti-inflammatory effect inhibiting NLRP3 inflammasome activation, showing advantages in reducing side effects, improving prognosis during FLD treatment, and improving the survival rate of patients. Moreover, the natural products, such as licochalcone B and cryptotanshinone, have the potential to be developed as inhibitors for treating FLD due to their specifically inhibiting NLRP3 inflammasome activation. However, the mechanisms underlying TCM inhibiting NLRP3 inflammasome activation have not yet been systematically studied and remain to be further investigated. The bioactive components of TCM are complex and many of them exhibit an anti-inflammation effect, but it is unknown whether there is synergistic or antagonistic interaction between these components. Moreover, most research based on animals and cells is urgently required to undergo clinical safety and efficacy studies. Collectively, even though further studies are required to disentangle the mechanism of TCM, we believe that TCM and its natural products are promising therapeutic applications for the treatment of FLD.

Author contributions

BZ, XG, XX, and ZY, supervised the project and acquired funding for the study; LT and LL collected the relevant literature, XG, LL, and LT designed the manuscript and pictures; LT wrote the manuscript; BZ, ZY, LTT, LLX, and XG revised the manuscript.

References

Adachi, Y., Bradford, B. U., Gao, W., Bojes, H. K., and Thurman, R. G. (1994). Inactivation of Kupffer cells prevents early alcohol-induced liver injury. *Hepatology* 20, 453–460. doi:10.1002/hep.1840200227

Al-Yahya, M., Mothana, R., Al-Said, M., Al-Dosari, M., Al-Musayeb, N., Al-Sohaibani, M., et al. (2013). Attenuation of CCl4-induced oxidative stress and hepatonephrotoxicity by Saudi sidr honey in rats. *Evid. Based. Complement. Altern. Med.* 2013, 569037. doi:10.1155/2013/569037

Arab, J. P., Arrese, M., and Trauner, M. (2018). Recent insights into the pathogenesis of nonalcoholic fatty liver disease. *Annu. Rev. Pathol.* 13, 321–350. doi:10.1146/annurev-pathol-020117-043617

Asrani, S. K., Devarthavhi, H., Eaton, J., and Kamath, P. S. (2019). Burden of liver diseases in the world. *J. Hepatol.* 70, 151–171. doi:10.1016/j.jhep.2018.09.014

Basiorcka, A. A., McGraw, K. L., Eksioglu, E. A., Chen, X., Johnson, J., Zhang, L., et al. (2016). The NLRP3 inflammasome functions as a driver of the myelodyplastic syndrome phenotype. *Blood* 128, 2960–2975. doi:10.1182/blood-2016-07-730556

Bataller, R., and Brenner, D. A. (2005). Liver fibrosis. *J. Clin. Investig.* 115, 209–218. doi:10.1172/JCI24282

Buo, Y., Chen, J., Liu, C., Wang, R., Han, X., Li, L., et al. (2022). Protective effect of danshen Zexie decoction against non-alcoholic fatty liver disease through inhibition of ROS/NLRP3/IL-1β pathway by Nrf2 signaling activation. *Front. Pharmacol.* 13, 877924. doi:10.3389/fphar.2022.877924

Brocker, C. N., Kim, D., Melia, T., Karri, K., Velenosi, T. J., Takahashi, S., et al. (2020). Long non-coding RNA Gm15441 attenuates hepatic inflammasome activation in response to PPARA agonism and fasting. *Nat. Commun.* 11, 5847. doi:10.1038/s41467-020-19554-7

Broz, P., and Dixit, V. M. (2016). Inflammasomes: Mechanism of assembly, regulation and signalling. *Nat. Rev. Immunol.* 16, 407–420. doi:10.1038/nri.2016.58

Cao, Y., Shi, J., Song, L., Xu, J., Lu, H., Sun, J., et al. (2022). Multi-omics integration analysis identifies lipid disorder of a non-alcoholic fatty liver disease (NAFLD) mouse model improved by xexe–baizhu decoction. *Front. Pharmacol.* 13, 858795. doi:10.3389/fphar.2022.858795

Carta, S., Tassi, S., Semino, C., Fossati, G., Mascagni, P., Dinarollo, C. A., et al. (2006). Histone deacetylase inhibitors prevent exocytosis of interleukin-1beta-containing secretory lysosomes: Role of microtubules. *Blood* 108, 1618–1626. doi:10.1182/blood-2006-03-014126

Chang, R. C., and So, K. F. (2008). Use of anti-aging herbal medicine, Lycium barbarum, against aging-associated diseases. What do we know so far? *Cell. Mol. Neurobiol.* 28, 643–652. doi:10.1007/s10571-007-9181-x

Chen, S., Zhou, H., Lin, M., Mi, R., and Li, L. (2013). Decoction vs extracts-mixed solution: Effect of yiqihuoxue formula on non-alcoholic fatty liver disease in rats. *J. Tradit. Chin. Med.* 33, 513–517. doi:10.1016/j.sciadj.2013.06.017

Cheng, D., and Kong, H. (2011). The effect of Lycium barbarum polysaccharide on alcohol-induced oxidative stress in rats. *Molecules* 16, 2542–2550. doi:10.3390/molecules16032542

Chiang, H., Lu, H. F., Chen, J. C., Chen, Y. H., Sun, H. T., Huang, H. C., et al. (2020). Adlay seed (Coix lacryma-jobi L.) extracts exhibit a prophylactic effect.
Liu et al. 10.3389/fphar.2022.967594

Frontiers in Pharmacology frontiersin.org 12

on diet-induced metabolic dysfunction and nonalcoholic fatty liver disease in mice. Evid. Based. Complement. Altern. Med. 2020, 2019:625. doi: 10.1155/2020/9519625

Kuemmerle-Deschner, J. B., Ramos, E., Blank, N., Rorslev, F., Felix, S. D., Jung, T., et al. (2011). Canaluminum (AC2885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). Arthritis. Res. Ther. 13 (1), R34. doi: 10.1186/ar3266

Crosas-Molist, E., and Fabregat, I. (2015). Role of NADPH oxides in the redox biology of liver fibrosis. Redox Biol. 6, 106–111. doi: 10.1016/j.redox.2015.07.005

Dang, Y., Xu, J., Yang, Y., Li, C., Zhang, Q., Zhou, W., et al. (2020). Long-gui-zhu-gan decoction alleviates hepatic steatosis through SOCS2 modification by N6-methyladenosine. Biomed. Pharmacother. 127, 109976. doi: 10.1016/j.biopha.2020.109976

Del Campo, J. A., Gallego, P., and Grande, L. (2018). Role of inflammatory response in liver diseases. Therapeutic strategies. World J. Hepatol. 10, 1–7. doi: 10.4253/wjh.v10.i1.1

Deng, M., Guo, H., Tam, J. W., Johnson, B. M., Brickley, W. J., New, J. S., et al. (2019). Biological and toxicological activities of Glycyrrhiza glabra L. (Fabaceae). doi: 10.1016/j.celrep.2020.108405

NLRP3 active conformation and inflammasome activation by promoting NLRP3 inflammasome activation and causes idiosyncratic hepatotoxicity. Cell. Commun. Signal. 19, 13. doi: 10.1186/s12967-020-00647-1

Gaul, S., Leszcynska, A., Albrecht, F., Kaufmann, B., Johnson, C. D., Adams, L. A., et al. (2021). Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. J. Hepatol. 74, 156–167. doi: 10.1016/j.jhep.2020.07.041

Granowitz, E. V., Vannier, E., Poutsiaka, D. D., and Dinarello, C. A. (1992). Effect of interleukin-1 (IL-1) blockade on cytokine synthesis: II. IL-1 receptor antagonist inhibits lipopolysaccharide-induced cytokine synthesis by human monocytes. Blood 79, 2364–2369. doi: 10.1182/blood.v79.8.2364

Halle, A., Hornung, V., Petzold, G. C., Stewart, C. R., Monks, B. G., Reinheckel, T., et al. (2008). The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat. Immunol. 9, 857–865. doi: 10.1038/ni.1636

Han, X., Song, J., Lian, L. H., Yao, Y. L., Shao, D. Y., Fan, Y., et al. (2018). Ginsenoside 25-OCH3(3)-PPD promotes activity of LXRs to ameliorate P2x7r-mediated NLRP3 inflammasome in the development of hepatic fibrosis. J. Agric. Food Chem. 66, 7023–7035. doi: 10.1021/acs.jafc.6b00982

Hao, Y. Y., Cui, W. W., Gao, H. L., Wang, M. Y., Liu, Y. L., C. R., et al. (2022). Lignida granules ameliorate the high-fat-diet induced liver injury in mice by antagonising hepatocytes pyroptosis. Pharm. Biol. 60, 274–281. doi: 10.1080/13880209.2022.209501

Heneo-Mejia, J., Elinav, E., Jin, C., Hao, L., Mehul, W. Z., Strewig, T., et al. (2012). Inflammasome-mediated obesity and the progression of NAFLD and obesity. Nature 482, 179–185. doi: 10.1038/nature10809

Hornung, V., Bauerfeind, F., Halle, A., Samstad, E. O., Kono, H., Rock, K., et al. (2008). Silica crystals and aluminium salts activate the NALP3 inflammasome through phagosomal destabilisation. Nat. Immunol. 9, 847–856. doi: 10.1038/ni.1631

Hou, L., Zhang, Z., Yang, L., Chang, N., Zhao, X., Zhou, X., et al. (2021). NLRP3 inflammasome priming and activation in cholestatic liver injury via the sphingosine 1-phosphate/S1P receptor 2/Gal1(12/13)/MAPK signaling pathway. J. Mol. Med. 99, 273–288. doi: 10.1007/s00109-020-02324-2

Huang, P., Yang, L., Liu, Y., Jiang, Y., Li, Y., Chen, Z., et al. (2022). Lanthan granules ameliorate nonalcoholic fatty liver disease by regulating the PPARa signaling pathway. Evid-Based Complement. Altern. Med. 2022, 1124901–1124915. doi: 10.1155/2022/1124901

Iracheta-Vellve, A., Petraske, J., Grygorski, B., Bala, S., Cui, T., Kodyš, K., et al. (2017). Interleukin-1 inhibition facilitates recovery from liver injury and promotes regeneration of hepatocytes in alcoholic hepatitis in mice. Liver Int. 37, 968–973. doi: 10.1111/liv.13430

Iracheta-Vellve, A., Petraske, J., Satsiachandran, A., Grygorski, B., Bala, S., Kodyš, K., et al. (2015). Inhibition of sterile danger signals, uric acid and ATP, prevents inflammasome activation and protects from alcoholic steatohepatitis in mice. J. Hepatol. 65, 1147–1155. doi: 10.1016/j.jhep.2015.06.013

Kanneganti, T. D., Lamkanfi, M., Kim, Y. G., Chen, G., Park, J. H., Franchi, L., et al. (2007). Pan nexin-1-mediated recognition of bacterial molecules activates the cryopyrin inflammasome independent of Toll-like receptor signaling. Immunity 26, 433–443. doi: 10.1016/j.immuni.2007.03.008

Ke, W., Wang, P., Wang, X., Zhou, H., Xu, H., and Chen, F. (2020). Dietary Platycodon grandiflorus attenuates hepatic insulin resistance and oxidative stress in high-fat-diet induced non-alcoholic fatty liver disease. Nutrients 12, E480. doi: 10.3390/nu1204E480

Koorn, J. W., Vree, A., Tacke, F., and Feldstein, A. E. (2020). The NLRP3 inflammasome in alcoholic and nonalcoholic steatosis. Semin. Liver Dis. 40, 298–306. doi: 10.1055/s-0040-1707540

Kubes, P., and Mehal, W. Z. (2012). Sterile inflammation in the liver. Gastroenterology 143, 1158–1172. doi: 10.1053/j.gastro.2012.09.008
Regulation of proinflammatory cytokines and hepatic steatosis in mice. *Hepatology* 54, 2185–2197. doi:10.1002/hep.24599

Mangkan, M. S. J., Ohlava, E. J., Routh, W. R., Seidel, H. M., Glick, G. D., and Latz, E. (2018). Targeting the NLRP3 inflammasome in inflammatory diseases. *Nat. Rev. Drug Discov.* 17, 688. doi:10.1038/nrd.2018.149

Masters, S. L., Dunne, A., Subramanian, S. L., Hull, R. L., Tannahill, G. M., Sharp, F. A., et al. (2010). Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1p in type 2 diabetes. *Nat. Immunol.* 11, 897–904. doi:10.1038/ni.1935

McClen, C., Cohen, D., Dinarello, C., Cannon, J., Sheddofsky, S., and Kaplan, A. (1986). Serum interleukin-1 (IL-1) activity in alcoholic hepatitis. *Life Sci.* 39, 1479–1485. doi:10.1016/0024-3205(86)90554-0

Mitsuyoshi, H., Yashu, K., Kari, H., Taketani, H., Ishida, H., Okajima, A., et al. (2017). Hepatic nucleotide binding oligomerization domain-like receptors pyrin domain-containing 3 inflammasomes are associated with the histologic severity of non-alcoholic fatty liver disease. *Hepatol. Res.* 47, 1459–1468. doi:10.1111/hepr.12883

Miura, K., Kodama, Y., Inokuchi, S., Schnabl, B., Aoyama, T., Ohashi, H., et al. (2010). Toll-like receptor 9 promotes steatochemistry by induction of interleukin-1β in mice. *Gastroenterology* 139, 323–334. doi:10.1053/j.gastro.2010.03.052

Neumann, K., Schiller, B., and Tiesg, G. (2018). NLRP3 inflammasome and IL-33: New players in sterile liver inflammation. *Int. J. Mol. Sci.* 19, E2732. doi:10.3390/ijms19092732

Nie, Y., Liu, Q., Zhang, W., Wan, Y., Huang, C., and Zhu, X. (2021). Ursolic acid reverses liver fibrosis by inhibiting NOX4/NLRP3 inflammasome pathways and bacterial dysbiosis. *Gut Microbes* 13, 1972-74. doi:10.1080/19490976.2021.1972746

Pan, M. X., Zheng, C. Y., Deng, Y. I., Tang, K. B., Nie, H., Xie, J., et al. (2021). Hepatic protective effects of Shengling Baizhu powder, a herbal compound, against inflammatory damage via TLR4/NLRP3 signalling pathway in rats with nonalcoholic fatty liver disease. *J. Integr. Med.* 19, 428–436. doi:10.3391/jim.2021.07.004

Pessione, F., Ramond, M. J., Peters, L., Pham, B. N., Batel, P., Rueff, B., et al. (2003). Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver Int.* 23, 45–53. doi:10.1046/j.1478-3275.2003.01804.x

Petraske, J., Bala, S., Caik, T., Lippai, D., Kody, K., Menasy, V., et al. (2012). IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J. Clin. Investig.* 122, 3476–3489. doi:10.1172/JCI60777

Petraske, J., Dolganusic, A., Caik, T., Kurt-Jones, E. A., and Saba, G. (2011). Type I interferons protect from Toll-like receptor 9-associated liver injury and regulate IL-1 receptor antagonist in mice. *Gastroenterology* 140, 697–708. doi:10.1053/j.gastro.2010.08.020

Petraske, J., Iarache-Vellve, A., Saha, B., Satischandran, A., Kody, K., Fitzgerald, K. A., et al. (2015). Metabolic danger signals, uric acid and ATP, mediate inflammatory cross-talk between hepatocytes and immune cells in alcoholic liver disease. *J. Leukoc. Biol.* 98, 249–256. doi:10.1016/j.jleukb.2014.11.012

Pimpin, L., Cortez-Pinto, H., Negro, F., Corbould, E., Lazarus, J. V., Webber, L., et al. (2018). Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. *J. Hepatol.* 69, 718–735. doi:10.1016/j.jhep.2018.03.011

Qiao, J. Y., Li, H. W., Liu, P. G., Li, Y. C., Tian, S., Cao, L. H., et al. (2019). Effects of Portulaca oleracea extract on acute alcoholic liver injury of rats. *Molecules* 24, E2887. doi:10.3390/molecules24162887

Qin, G., Ma, J., Huang, Q., Yin, H., Han, J. L., Li, M., et al. (2018). Isoquercetin improves hepatic lipid accumulation by activating AMPK pathway and suppressing TGF-β signaling on an HFD-induced nonalcoholic fatty liver disease rat model. *Int. J. Mol. Sci.* 19, E4126. doi:10.3390/ijms19124126

Ratnani, V., Shekh, M. Y., Sanyal, A. J., Lim, J. K., Conjeevaram, H., Chalasani, N., et al. (2012). A phase 2, randomized, double-blind, placebo-controlled study of GS-4904 in subjects with nonalcoholic steatohepatitis. *Hepatology* 55, 419–428. doi:10.1002/hep.24477

Rostamizadeh, P., Asl, S., Faz, G., Ahmadijoo, P., Mahmodudin, T., Bokov, D. O., et al. (2012). Effects of licorice root supplementation on liver enzymes, hepatic steatosis, metabolic and oxidative stress parameters in women with nonalcoholic fatty liver disease: A randomized double-blind clinical trial. *Phytotherapy Res.* 26, 1046–1050. doi:10.1038/s41395-018-0030-4

Sanyal, A. J., Chalasani, N., Kowdley, K. V., McCullough, A., Diehl, A. M., Bass, N. M., et al. (2010). Figitolizam, vitamin E, or placebo for nonalcoholic steatohepatitis. *N. Engl. J. Med.* 362, 1675–1685. doi:10.1056/NEJMoa0979229
Shang, Y., Jiang, M., Chen, N., Jiang, X. L., Zhan, Z. Y., Zhang, Z. H., et al. (2022). Inhibition of HMGB1/TLR4 signaling pathway by digitigalnine: A potential therapeutic role in alcoholic liver disease. J. Agric. Food Chem. 70, 2806–2893. doi:10.1021/acs.jafc.2c00315

Shen, T., Lei, T., Chen, L., Zhu, B. B., Xu, B. L., Zhang, C. P., et al. (2021). Gardosinde hinders caspase-1-mediated hepatocyte pyroptosis through the CTCF/DPPA signaling pathway. Front. Physiol. 12, 669202. doi:10.3389/fphys.2021.669202

Shi, H., Zhang, Y., Xing, J., Liu, L., Qiao, F., Li, J., et al. (2020). Raucin attenuates hepatic injury in non-alcoholic steatohepatitis cell model by suppressing inflammasome-dependent GSDMD-mediated cell pyroptosis. Int. Immunopharmacol. 81, 106195. doi:10.1016/j.intimp.2020.106195

Shi, W., Xu, G., Zhan, X., Gao, Y., Zhang, Z., Fu, S., et al. (2020). Carnosol inhibits inflammasome activation by directly targeting HSP90 to treat inflammation-mediated diseases. Cell. Death Dis. 11, 252. doi:10.1038/s41419-020-02460-x

Silva, L., Rausch, V., Seitz, H. K., and Mueller, S. (2017). Does hypoxia cause carcinogenic iron accumulation in alcoholic liver disease (ALD)? Cancers (Basel) 9, E145. doi:10.3390/cancers9110145

Song, H. M., Li, X., Liu, Y. Y., Liu, W. P., Cui, Z. H., Zhou, L., et al. (2018). Carnosic acid protects mice from high-fat diet-induced NAFLD by regulating MARGCS. Int. J. Mol. Med. 42, 193–207. doi:10.3892/ijmm.2018.3593

Szabo, G., and Csak, T. (2012). Inflammases in liver diseases. J. Hepatol. 57, 642–654. doi:10.1016/j.jhep.2012.03.035

Szabo, G., Dolganiuc, A., and Mandrekar, P. (2006). Pattern recognition receptors: A contemporary view on liver diseases. Hepatology 44, 289–297. doi:10.1002/hep.21338

Takeuchi, O., and Akira, S. (2010). Pattern recognition receptors and inflammation. Cell. 140, 805–820. doi:10.1016/j.cell.2010.01.022

Tang, X., Olatunji, O. J., Zhou, Y., and Hou, X. (2017). Allium tuberosum: Antidiabetic and hepatoprotective activities. Food Res. Int. 102, 681–689. doi:10.1016/j.foodres.2017.08.034

The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1980-2017: A systematic analysis for the global burden of disease study 2017. Lancet. Gastroenterol. Hepatol. 5 (2020) 245–266. doi:10.1016/S2468-1259(19)30349-8

Thurz, M. R., Richardson, P., Allison, M., Austin, B., Bowers, M., Day, C. P., et al. (2015). Predisolone or pentoxifylline for alcoholic hepatitis. N. Engl. J. Med. 372, 1619–1628. doi:10.1056/NEJMoa1412279

Tigl, H., Moschen, A. R., and Szabo, G. (2016). Interleukin-1 and inflammasomes in alcoholic liver disease/acute alcoholic hepatitis and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Hepatology 64, 955–965. doi:10.1002/hep.28486

Tigl, H., Wilmer, A., Vogel, W., Herold, M., Nolchen, B., Judmaier, G., et al. (1992). Serum levels of cytokines in chronic liver diseases. Gastroenterology 103, 264–274. doi:10.1016/0016-5085(92)91122-k

Tzimolas, K., Athyros, V. G., Paschos, P., and Karagiannis, A. (2015). Nonalcoholic fatty liver disease and steatosis. Metabolism 64, 1215–1223. doi:10.1016/j.metabol.2015.07.003

Wang, C. M., Yuan, R. S., Zhang, W. Y., Sun, J. H., Wu, Y. J., Li, H., et al. (2016). Schisandra polysaccharide inhibits hepatic lipid accumulation by downregulating expression of SREBP in NAFLD mice. Lipids Health Dis. 15, 193. doi:10.1186/s12944-016-0358-5

Wang, F., Park, J. S., Ma, Y., Ma, H., Lee, Y. J., Lee, G. R., et al. (2021). Ginsenoside Rg1 protects against non-alcoholic fatty liver disease by ameliorating lipid peroxidation, endoplasmic reticulum stress, and inflammatory responses and liver immunology. Gastroenterology. 105, 274–281. doi:10.1053/j.gastro.2021.05.034

Xu, G., Tu, S., Zhan, X., Wang, Z., Zhang, P., Shi, W., et al. (2021). Echinatin effectively protects against NAFLD inflammasome-driven diseases by targeting HSP90. JCI Insight 6, 134601. doi:10.1172/jci.insight.134601

Xu, N., Wu, X., Luo, H., Xu, F. F., Huang, Q. H., Wu, J. Z., et al. (2020). Patchouli Oil attenuates high fat diet-induced non-alcoholic hepatic steatosis. Phytomedicine. 133, 102874. doi:10.1016/j.phymed.2020.102874

Xu, Y., Yang, C., He, X., Zhao, J., and Huang, W. (2018). Ginsenoside Rgl protects against non-alcoholic fatty liver disease by amelowering lipid peroxidation, endoplasmic reticulum stress, and inflammasome activation. Drug Metab. Dispos. 46, 1310–1319. doi:10.1124/dmd.118.082008

Yang, C., He, X., Zhao, J., and Huang, W. (2021). Hepatoprotection by Ginsenoside Rg1 in alcoholic liver disease. Int. Immunopharmacol. 92, 107327. doi:10.1016/j.intimp.2020.107327

Yang, J., Ma, W., Mei, Q., Song, J., Shu, L., Zhang, S., et al. (2020). Protective effect of fuizhi Licheng decoction against non-alcoholic fatty liver disease via anti-inflammatory response through regulating p35 and PPAR signaling. Biol. Pharm. Bull. 43, 1623–1633. doi:10.1248/bpb.20.00053

Yang, J. M., Sun, Y., Wang, M., Zhang, X. L., Zhang, S. J., Gao, Y. S., et al. (2019). Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J. Gastroenterol. 25, 5105–5119. doi:10.3748/wjg.v25.i34.5105

Yang, M., Li, X., Zeng, X., Ou, Z., Xue, M., Gao, D., et al. (2016). Rheum palmatum L. Attenuates high fat diet-induced hepatosteatosis by activating AMP-activated protein kinase. Am. J. Chin. Med. 44, 551–564. doi:10.1142/S0192415x16500300

Yang, Q. H., Xu, Y. J., Liu, Y. Z., Liang, Y. J., Feng, G. F., Zhang, Y. P., et al. (2014). Effects of Chaubai-shugan-san and shen-ling-Bai-Zhu-San on p38 MAPK pathway in kupffer cells of nonalcoholic steatohepatitis. Evid. Based. Complement. Altern. Med. 2014, 670133. doi:10.1155/2014/670133
Yen, I. C., Lin, J. C., Chen, Y., Tu, Q. W., and Lee, S. Y. (2020). Antrodia cinnamomea attenuates non-alcoholic steatohepatitis by suppressing NLRP3 inflammasome activation in vitro and in vivo. *Am. J. Chin. Med.* 48, 1859–1874. doi:10.1142/S0192415X20500937

Younossi, Z., Anstee, Q. M., Marietti, M., Hardy, T., Henry, L., Eslam, M., et al. (2018). Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. *Nat. Rev. Gastroenterol. Hepatol.* 15, 11–20. doi:10.1038/nrgastro.2017.109

Zhang, B., Xu, D., She, L., Wang, Z., Yang, N., Sun, R., et al. (2018). Silybin inhibits NLRP3 inflammasome assembly through the NAD(+)⁄SIRT2 pathway in mice with nonalcoholic fatty liver disease. *Faseb J.* 32, 757–767. doi:10.1096/fj.20170662R

Zhang, C. H., Xiao, Q., Sheng, J. Q., Liu, T. T., Cao, Y. Q., Xue, Y. N., et al. (2020). Gegen Qinlian Decoction abates nonalcoholic steatohepatitis associated liver injuries via anti-oxidative stress and anti-inflammatory response involved inhibition of toll-like receptor 4 signaling pathways. *Biomed. Pharmacother.* 126, 110076. doi:10.1016/j.biopha.2020.110076

Zhang, H. Y., Tian, J. X., Lian, F. M., Li, M., Liu, W. K., Zhen, Z., et al. (2021). Therapeutic mechanisms of traditional Chinese medicine to improve metabolic diseases via the gut microbiota. *Biomed. Pharmacother.* 133, 110857. doi:10.1016/j.biopharma.2020.110857

Zhang, Q., Ma, C., Duan, Y., Heinrich, B., Rosato, U., Diggs, L. P., et al. (2021). Gut microbiome directs hepatocytes to recruit MDSCs and promote cholangiocarcinoma. *Cancer Discov.* 11, 1248–1267. doi:10.1158/2159-8290.CD-20-0304

Zhu, K., Guo, Y., Zhao, C., Kang, S., Li, J., Wang, L., et al. (2021). Etiology exploration of non-alcoholic fatty liver disease from traditional Chinese medicine constitution perspective: A cross-sectional study. *Front. Public Health* 9, 635818. doi:10.3389/fpubh.2021.635818

Zhu, R., Ou, Z., Ruan, X., and Gong, J. (2012). Role of liver X receptors in cholesterol efflux and inflammatory signaling (review). *Mol. Med. Rep.* 5, 895–900. doi:10.3892/mmr.2012.758

Zhu, Z., Hu, R., Li, J., Xing, X., Chen, J., Zhou, Q., et al. (2021). Alpinetin exerts anti-inflammatory, anti-oxidative and anti-angiogenic effects through activating the Nrf2 pathway and inhibiting NLRP3 pathway in carbon tetrachloride-induced liver fibrosis. *Int. Immunopharmacol.* 96, 107660. doi:10.1016/j.intimp.2021.107660

张欢, 孔晨帆, 杨佳潞, 周艳彩, 和孙劲晖. 肝性肝纤维化的中西医结合治疗思路 (2022). 中西医结合肝病杂志 32, 167–169.