REVIEW
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Research progress on the mechanism of traditional Chinese medicine in the treatment of autoimmune hepatitis

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Jing Chen developed the idea for the study and provided assistance in the writing of the article and improved the quality of the paper; Si-Qi Wen, Yu-Hui Wang performed the Literature search; Kun-Ling Chen and Yi-Hua Fan wrote original draft the paper; Qing Wen was responsible for figures and tables in the paper.

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Abbreviations
AIH, Autoimmune hepatitis; TCM, traditional Chinese medicine; Con A, cutinoglobulin A; TFT, total flavonoids of trichothecene extract Tetrastigma hemsleyanum; PI3K, The phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin protein; SA-A, Salvia divinorum extract salvianolic acid A; OPs, oyster protein hydrolysates; LUT, Luteolin-7-o-rutinoside; TLRs, Toll-like receptors; My D88, myeloid differentiation factor; TAK1, TGF-β activated kinase; PHI, Phillygenin; LX-2, human liver astrocyte called Lieming Xu-2; LPS, lipopolysaccharide; Nrf2, nuclear factor-erythroid 2-related factor 2; GS, Liver Sharp granules.

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Abstract
Autoimmune hepatitis is an inflammatory liver disease primarily mediated by T cell. It has not been fully elucidated about the pathogenesis, and it is presently thought to be related to genetic susceptibility, infection and environmental triggers, and abnormal autoimmune regulation. Recent studies have found that traditional Chinese medicine can improve the biochemical indicators and clinical symptoms of patients with autoimmune hepatitis. This article reviews the specific mechanism of traditional Chinese medicine on treating autoimmune hepatitis in order to propose new ideas for its clinical diagnosis and treatment.

Keywords: traditional Chinese medicine; autoimmune hepatitis; mechanism of action; research progress

Background

Autoimmune hepatitis (AIH), which is characterized by immune injury, is a chronic, progressive inflammatory of liver. This disease is marked by hypergammaglobulinemia, the presence of autoantibodies and inflammation within the liver, and includes pathological changes like lymphocytic infiltration and interface hepatitis [1]. AIH is predominantly female and can occur at any age and in any race [2]. The exact physiopathologic mechanisms remain unclear and are generally thought to be related to genetics and epigenetics, aberrant autoimmune regulatory mechanisms, and environmental triggers [3]. The continued progression of autoimmune hepatitis without intervention can result in liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. How to effectively treat autoimmune hepatitis, block or delay its progression, and prevent its further development into advanced liver diseases has emerged as a highly researched and crucial area within the field of liver diseases. Abnormal immune responses that target liver autoantigens and induce persistent and self-perpetuating liver inflammation are the pathogenic mechanisms of autoimmune hepatitis [4]. The aim of current treatments is to induce and maintain long-term remission of hepatic inflammation, thereby relieving symptoms and halting or even reversing liver injury and fibrosis and the standard treatment for it is steroids combined with azathioprine [4, 5]. However, progression may still occur even in patients who are effectively treated with steroids combined with azathioprine. Other immunosuppressive agents such as mortimecoxib, d-penicillamine, sirolimus, and anti-T-cell therapies have been used in refractory cases gaining little success [6]. Unstable or refractory disease and frequent relapses have prompted the use of liver transplantation as a last treatment option. Therefore, seeking safer and more effective traditional Chinese medicine for autoimmune hepatitis is a future trend.

For the past few years, the clinical application of TCM has achieved good results in treating autoimmune hepatitis. The biochemical indexes and TCM symptom scores of autoimmune hepatitis patients improved significantly after TCM treatment, but the mechanism remains unclear. This article reviews the specific mechanism of Chinese medicine in treating AIH.

Traditional Chinese medicine can adjust the Th17/Treg immune imbalance

Th17/Tregs immune imbalance is considered to be a key pathological factor in the pathogenesis of immune-mediated autoimmune hepatitis [7]. Dysregulation of Th17 cell differentiation and activity brings more autoimmune diseases [8]. In addition, Th17 cells secrete inflammatory factors such as IL-17, IL-22 and TNF-α, and IL-17 induces the expression of IL-6 through the MAPK pathway in hepatocytes, and further stimulates Th17 to form a positive feedback loop to exacerbate the inflammatory response, inducing immune cell infiltration and liver injury, driving liver inflammation and promoting autoimmune hepatitis [9]. In contrast, Tregs have the function of maintaining immune tolerance and preventing attack from autoimmune disease, that is mainly achieved by controlling self-reactive T cells and releasing anti-inflammatory cytokines to suppress inflammation [10]. Tregs also express negative regulatory cell surface receptors like LAG3 and CTLA4 to down-regulate immune cell activation [11]. The immune response suppression by Tregs is achieved through the release of immunosuppressive cytokines such as IL-10, TGF-β, and IL-35, whereas Th17 inhibits Treg function by producing IL-17 [12]. Furthermore, upregulation of the Th17/Treg ratio can accelerate the progress of liver fibrosis [13]. Therefore, modulation of Th17/Treg balance to regulate autoimmunity, improve hepatic inflammatory response, and reverse liver fibrosis has become a new strategy for autoimmune hepatitis treatment. Currently, research concerning the treatment of autoimmune hepatitis based on the regulation of Th17/Treg balance by traditional Chinese medicine (TCM) has made great progress.

Wang et al. have found that Bu Xu Hua Yu recipe (consist of Dried *Rehmanniae Radix Praeparata*, *Angelicae Sinensis Radix*, *Astragali Radix*, *Paeoniae Radix Alba*, *Chuanxiong Rhizoma* and *Sedum Rhizoma*) could regulate TGF-β expression by increasing IL-10 expression and decreasing IL-17 expression, elevating the level of Treg cells and decreasing that of Th17 cells, thus regulating the Treg/Th17 immune imbalance, and ameliorating α-GalCer-induced hepatitis in mice [14]. And the formula can significantly suppress the expression of RORγt mRNA in liver tissues of AIH mice, reduce the role of RORγt protein in inhibiting the development and proliferation of Th17 cells. Moreover, it could regulate the development and proliferation of Treg cells and Th17 cells by increasing the expression of Foxp3 while decreasing the expression of RORγt. All above lead to regulating the Treg/Th17 immune imbalance and achieving the purpose of treatment of autoimmune hepatitis. Ji et al. intervened in mice with autoimmune hepatitis modeled by cutinoglobulin A (Con A) with total flavonoids of trichothecene extract *Tetrastigma hemsleyanum* (TFT) [15]. Results showed that TFT reduced inflammatory factors IL-17 and IL-6 levels in serum, and the proportion of splenic Th17 cells in autoimmune hepatitis mice. In the meantime, TFT increased the percentage of splenic Treg cells and the expression of Foxp3 in liver tissue and the serum levels of TGF-β1 and IL-10. It is known that TFT exerts anti-inflammatory effects to treat autoimmune hepatitis by regulating Treg/Th17 immune homeostasis. Tongluo Soft Firmness capsule, which is composed of *Astragali Radix*, *Fritillariae Cirrhosae Bulbus*, *Andrographis Herba*, *Salviae Miltiorrhizae Radix et Rhizoma*, and other traditional Chinese medicines, has the effect of invigorating the function of qi and the spleen, promoting blood circulation for removing obstruction in collaterals, resolving phlegm and softening softening hardness. Study showed that Tongluo RuanJian capsule could reduce the expression of serum Th17, increase the expression of Treg, and reduce the ratio of Th17/Treg, which confirmed that Tongluo RuanJian capsule could regulate the levels of Treg and Th17, enhance the immune function of the body, improve the hepatic function, and then inhibit the process of hepatic fibrosis [16]. Liu et al. investigated the interventional effect of Jianpi Qinghua recipe (made up of zedoary, raw astragalus, grass jelly, red peony, and lotus leaf) on peripheral blood regulatory T cell subsets in autoimmune hepatitis patients, and found that Jianpi Qinghua recipe reduced TNF-a expression, increased IL-10 expression, and promoted Th1/Th2 expression, and up-regulated the ratio of $CD4^+CD25^+$ Tregs, thus maintaining the balance between Tregs and effector cells in terms of function and number, and thus achieving the regulation of inflammation and immunity of AIH and improving the liver injury [17].

Chinese herbs and monomers can regulate the PI3K/AKT/mTOR signaling pathway

The phosphatidylinositol 3-kinases (PI3Ks) family of proteins is engaged in the regulation of various cellular functions, such as cell proliferation, differentiation, apoptosis, and metabolism. The major effector downstream of PI3K is protein kinase B（AKT）. The activation of PI3K can generate the second messenger PIP3 on the plasma membrane, thereby promoting the recruitment of proteins with pleckstrin homolgy domain to the plasma membrane and the subsequent activation of the signaling cascade. PDK1 phosphorylates AKT protein threonine at position 308 (T308), leading to partial activation of AKT, and activation of AKT phosphorylates its downstream targets like MDM2, TSC2, GSK3, FOXO, mTOR, and other downstream factors, thereby regulating the function of cells [18]. The downstream target of PI3K/AKT is mammalian target of rapamycin protein (mTOR). TSC1/2 (tuberous sclerosis complex) phosphorylated by AKT, prevents its negative regulation of the small G protein Rheb (Ras homology enriched in the brain), which drives Rheb enrichment and activation of the mTOR complex (mTORC1) in return [19]. Animal experiments have suggested that the PI3K/AKT/mTOR

signaling pathway can regulate hepatocyte apoptosis and autophagy, thereby ameliorating cutin A (Con a)-induced autoimmune hepatitis [20].

Salvia divinorum extract called salvianolic acid A (SA-A) prevents stimulation of hepatic stellate cells by suppressing the PI3K/AKT/mTOR signaling cascade, as well as extracellular matrix synthesis, and prevents apoptosis of hepatocytes by modulating the Bcl-2/Bax and caspase-3/cleaved caspase-3 signaling pathways [21]. Ginseng polysaccharides can improve hepatocyte apoptosis by inducing the PI3K / AKT and TLR / NF-κB signaling pathways, thereby inhibiting inflammation and hepatocyte apoptosis to attenuate the inflammatory response in autoimmune hepatitis [22]. Ginsenoside Rg3 can attenuate oxidative stress and inflammation by activating the PI3K/AKT signaling pathway, thereby attenuating hepatocyte necrosis and apoptosis [23]. Oyster protein hydrolysates (OPs) from oyster extracts were shown to be effective against inflammatory responses (IL-1β, IL-6, and TNF-α), and expression of inflammation-related proteins (MIP-2 and COX-2), which was concerned in suppressing the activation of the ERK/NF-κB signaling pathway and the PI3K/AKT signaling pathway [24]. Thus, it can be concluded that by modulating the ERK/NF-κB and PI3K/AKT-related signaling pathways, OPs inhibit oxidative damage, inflammatory responses, and hepatocyte apoptosis, thereby reducing liver injury. Luteolin-7-o-rutinoside (LUT), a flavonoid extract from *Pteris cretica* L. *var. nervosa*, was able to inhibit the PI3K/AKT/AMPK/NF-κB signaling pathway to alleviate LPS/D-gal-induced acute liver injury [25]. It can also down-regulate the expression of NF-κB inhibitor protein through PI3K/AKT pathway, promoting phosphorylation of NF-κB in the treatment of liver injury indirectly. Thus, we suppose LUT may let inflammation under control by inhibiting TLR4 signaling and its downstream NF-κB expression. An-Gong-Niu-Huang Wan, a composite prescription in TCM, is made up of *Bovis Calculus*, *Bubali Cornu*, *Moschus*, *Margarita*, *Cinnabaris*, *Realgar*, *Coptidis Rhizoma*, *Scutellariae Radix*, *Gradeniae Fructus*, *Radix Curcumae*, and *Borneolum Synthcticum*. Study revealed that it could reduce the inflammatory reaction through the devitalized MAPK and PI3K/Akt signaling pathways and the resulting blocking of NF-κB activation [26]. Study found that the expression level of P53 in liver tissues of Pien Tze Huang (PZH)-intervened mice decreased significantly, while the protein amounts of ERK1/2, Akt, p-Akt, and PI3K increased significantly [27]. It is suggested that PZH can effectively inhibit the activation of mTOR signaling pathway in AIH mice, thus improving the liver function of Con A-induced AIH mice. We showed the intervening effects of the above herbal active ingredients on the PI3K/AKT/mTOR signaling pathway in Figure 1.

TCM monomers regulate TLRs signaling pathways

Toll-like receptors (TLRs) found in dendritic cells and macrophages, are a class of receptors that are able to mediate recognition of and response to foreign pathogens. They recognize different pathogen-related molecular patterns and play an essential part in the natural immune response. They are the first defensive line against pathogen invasion and act a crucial part in inflammation, as well as regulation, survival, and proliferation of immune cells. Activation of the TLRs signaling pathway roots in the structural domain of the cytoplasmic Toll/IL-1 receptor (TIR), which interacts with the adaptor proteins called myeloid differentiation factor (My D88) contained in the Toll/IL-1 receptor structural domain. Activated TLRs recruit My D88, then activates IL-1 receptor-associated kinase (IRAK) and TGF-β activated kinase (TAK1), which in turn stimulates the IkB kinase cascade and activates the nuclear transcription factor NF-κB, resulting in the expression of cytokines like IL-1β, TNF-α and others related to inflammation and immunity and the production of a mass of inflammatory cytokines such as IL-1β and TNF-α ultimately [28, 29].

Study found in mice that after pretreated with *Rabdosia amethystoides* (Benth.) Hara (ERA), which is an extract of traditional Chinese medicine, the levels of AST, ALT, TNF-α, INF-γ, and IL-6 were remarkablely decreased, the degree of hepatic necrosis was significantly attenuated, and the expression of both TLR4 mRNA and TLR8 proteins were also dramatically down-regulated, which indicated the hepatoprotective properties of ERA against Con A-induced liver injury [30]. The inhibition of oxidative stress and the release of inflammatory mediators like TNF-α, INF-γ and IL-6 cintributes to its hepatoprotective effect, which may be mediated by the down-regulation of TLR4 expression and the inhibition of NF-κB activation. Phillygenin (PHI) can inhibit human liver astrocyte (Lieming Xu-2，LX-2) activation and fibrotic cytokine expression by suppressing lipopolysaccharide (LPS)-induced proinflammatory responses. Studies

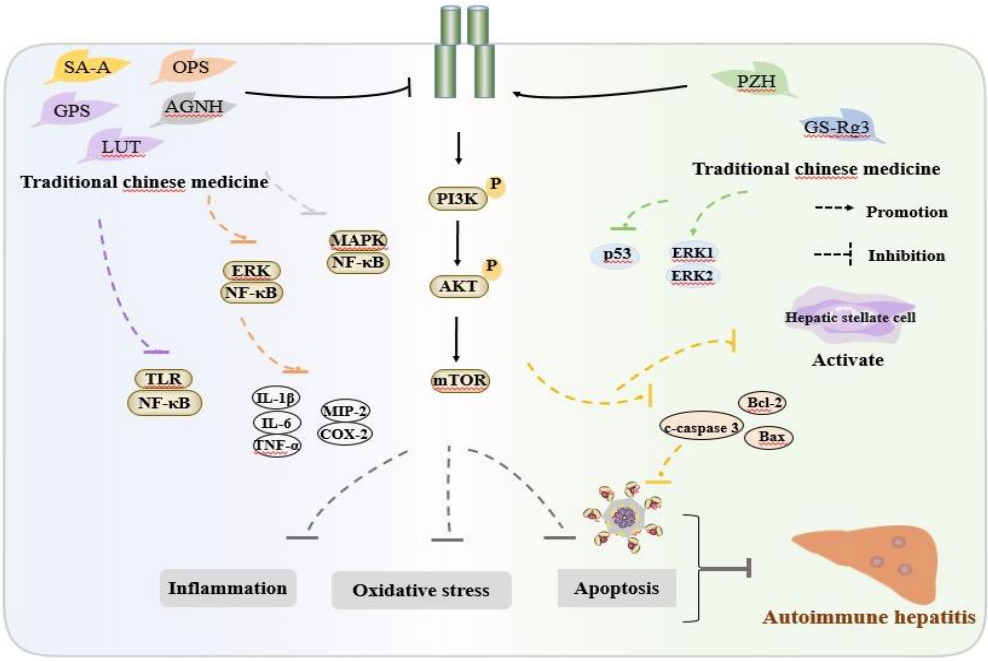

Figure 1 Mechanism of active ingredients of traditional Chinese medicine intervening in PI3K/AKT/mTOR signaling pathway. SA-A, *Salvia divinorum* extract salvianolic acid A; GPS, Ginseng polysaccharides; Gs-Rg3, ginsenoside Rg3; OPs, oyster protein hydrolysates; LUT, Luteolin-7-o-rutinosid; AGNH, An-Gong-Niu-Huang Wan; PZH, Pien Tze Huang.

showed that LX-2 cells were activated and expressed a huge amount of inflammatory and fibrotic cytokines in response to LPS stimulation [31]. PHI inhibited the expression of inflammatory and fibrotic factors by targeting TLR4, MyD88, TAK1, p65, p-p65, pIκBα, and IKKβ through the TLR4/MyD88/NF-κB signaling pathway, thereby suppressing LX-2 cell activation and taking anti-fibrotic effects. *Lavandula angustifolia* flavonoids (kurarinol A, 1) and ethyl acetate (EtOAc) extracted from *Sophora flavescens* Ait., suppressed IL-1β, TLR2, COX-2, and NF-κB (p65/p-p65) via the TLR2/NF-κB signaling pathway and were able to up-regulate the mRNA expression of SOD2, Nrf2, and OH-1 and down-regulate IL-1β in liver tissues, to inhibit inflammatory responses and attenuate oxidative stress. It can suppress inflammatory responses and alleviate oxidative stress, and take hepatoprotective effects [32]. The Chinese medicine *Gelsemium elegans* can attenuate Con A-induced AIH, nuclear factor-erythroid 2-related factor 2(Nrf2), and NF-κB signaling pathways, as well as the intestinal microbiota are involved in hepatoprotective effects [33]. The Chinese medicine *Livistona chinensis* fruit can inhibit TLR4/NF-κB signaling, and at the same time, activate Nrf2/HO-1 signaling, thus realizing hepatoprotective effects [34]. Studies showed that *Acanthopanax senticosus* polysaccharide (ASPS) was able to down-regulate the relative expression of TLR4 and MyD88 proteins, reduce the expression of p-NF-κB p65/NF-κB p65b, attenuate inflammatory responses, and alleviate the pathological changes in liver tissues, and its molecular mechanism may be concerned in the suppression of TLR4/MyD88 signaling pathway [35]. The interfering effects of the above TCM active ingredients on AIH-related signaling pathways are summarized in Table 1.

Modulation of gut flora by herbal monomers

The gut microbiota can coexist harmoniously with the host and has significant effects on its pathological and physiological processes, such as aiding in digestion and absorption of nutrients and keeping immune system stable [36]. Numerous studies have indicated that dysregulation of the gut microbiota takes an essential role in immune-mediated diseases [37, 38]. Autoimmune hepatitis is strongly linked to alterations in the structure of the commensal microbiota as well as activation of the aberrant immune system by microbial signals (mainly via the enterohepatic axis) [39]. The disruption of the intestinal barrier, translocation of the gut microbiota, and breakdown of immune homeostasis are closely associated with the onset and progression of autoimmune hepatitis [40, 41]. In the presence of a failing intestinal barrier, even bacteria that are beneficial under normal physiological circumstances can trigger inflammation and cause organ damage [42]. Increased intestinal permeability brings about the influx of microbe-associated molecular patterns (MAMPs) into the the body's circulation, stimulating an immune response. MAMP originating from the gut, such as lipopolysaccharides or microbial RNA, can reach the liver through the portal circulation, inducing hepatic inflammation and fibrosis [43–45].

Liquiritin, an active ingredient derived from the traditional Chinese medicine licorice, has demonstrated significant inhibitory effects on the growth of various pathogenic bacteria, such as *Bacillus sp.* 46, *Veillonella sp.* 31 and 48, *Bacteroides sp.* 22 and 57, and *Clostridium sp.* 51, while it has less effect on the growth of commensal probiotics (e.g., *Lactobacillus* and *Bifidobacterium*) [46]. The proprietary Chinese medicine Liushen capsule, which is composed of artificial musk and artificial boswelliae, was able to significantly increase the abundance of anaerobic bacteria like *Bifidobacterium* and *Lactobacillus* in the intestine while decreasing the abundance of some opportunistic pathogenic microorganisms in the intestine [47]. In addition, ginseng extract and sour date kernel dramatically increased the relative abundance of *Lactobacillus* and *Bifidobacterium*, while decreasing the relative abundance of *Streptococcus*, *Escherichia coli-Shigella*, and *Enterococcus* in rats, indicating that sour date kernel extract can balance the structure and diversity of the intestinal bacterial flora and has benefit to autoimmune hepatitis diversity and play a therapeutic role in autoimmune hepatitis [48]. The proprietary

Table 1 The signal pathway of AIH interfere by the effective components of traditional Chinese medicine

Animal models	TCM	Category	Target/signal pathways	References
α-Galcer	Bu Xu Hua Yu recipe	Decoction of herbal medicine	Foxp3, RORγt, IL-10, IL-17, TGF-β	[14]
Con-A	TFT	Tetrastigma hemsleyanum	Foxp3, RORγt, IL-17, IL-6, TGF-β1, IL-10	[15]
CCl4	SA-A	Danshen	PI3K/AKT/mTOR, Bcl-2/Bax, caspase-3/cleaved caspase-3	[21]
ConA	Ginseng polysaccharides	Ginseng	PI3K/AKT, TLR/NF-κB, TNF-α	[22]
APAP	Ginsenoside Rg3	Ginsenoside	PI3K/AKT, ALT, AST, TNF-α, IL-1β, GSH, MDA, CYP2E1, 4-HNE	[23]
Cd	OPs	Oyster protein hydrolysates	ERK/NF-κB, PI3K/AKT, IL-1β, IL-6, TNF-α, MIP-2, COX-2	[24]
LPS/D-gal	LUT	*Pteris cretica* L. *var. nervosa*	PI3K/AKT/AMPK/NF-κB, TLR4	[25]
HgS, As2S2	An-Gong-Niu-Huang Wan	Decoction of herbal medicine	MAPK, PI3K/Akt, NF-κB	[26]
Con A	Pien Tze Huang	Decoction of herbal medicine	mTOR, ERK1/2, Akt, p-Akt, PI3K, P53	[27]
Con A	ERA	*Rabdosia amethystoides* (Benth) Hara	TLR4, NF-κB, TNF-α, INF-γ, IL-6	[30]
LPS	PHI	Forsythia suspensa	TLR4/MyD88/NF-κB, TLR4, MyD88, TAK1, p65, p-p65, pIκBα, IKKβ	[31]
CCl4	Kurarinol A, 1, EtOAc	Sophora flavescens	TLR2/NF-κB, IL-1β, TLR2, COX-2, NF-κB (p65/p-p65), SOD2, Nrf2, OH-1, IL-1β	[32]
Con A	Koumine	*Gelsemium elegans*	Nrf2, NF-κB, ROS, MDA	[33]
LPS + D-GalN	FLCF	*Livistona chinensis* fruit	TLR4/NF-κB, Nrf2/HO-1	[34]
LPS + FCA + BCG	ASPS	*Acanthopanax senticosus* polysaccharide	TLR4, MyD88, p-NF-κB, p65/NF-κB, p65b	[35]

Chinese medicine, Liver Sharp granules (GS, composed of *Codonopsis Radix*, *Bupleuri Radix*, *Paeoniae Radix Alba*, *Angelicae Sinensis Radix*, *Poria*, *Atractylodis Macrocephalae Rhizoma*, *Citrus Aurantium Citri Reticulatae*, *Dandelionae Radix et Rhizoma*, *Dioscoreae Rhizoma*, *Polygonati Rhizoma*), has ability to modulate the dysbiosis of the intestinal flora, thereby attenuating CCl4-induced hepatic fibrosis. Immunohistochemical staining revealed that GS caused an increase in the expression of tight junction-associated proteins in the intestinal mucosa. 16S rRNA sequencing revealed that GS rebalanced intestinal dysbiosis by increasing the α and β diversity of the intestinal flora, reducing the ratio of thick-walled bacteria to anaplastic bacteria, and regulating the relative abundance of various bacteria [49]. Taken together, GS reduced intestinal permeability and rebalanced the intestinal microbiota to alleviate oxidative stress and inflammation, which ultimately attenuated CCl4-induced liver fibrosis. Therefore, it is hypothesized that Liver Sharp granules may treat autoimmune hepatitis by regulating the intestinal microecology.

In summary, Chinese medicine is safe and effective in treating autoimmune hepatitis through multiple signaling pathways, but some problems still exist. First of all, there are many current studies on the treatment of autoimmune liver disease by TCM, but most of them are animal experiments, and the clinical practice application is quite different from the animal experiments, so we should try to carry out clinical trials to prepare for its application in the clinic. Moreover, traditional Chinese medicine formulas are usually composed of many Chinese medicines, as well as single Chinese medicines' active ingredients are complex, and they react with each other during the boiling process, and need to undergo a complex metabolic process after being absorbed by the human body, so it is difficult to explain the role of a single component in a formula when researching the particular mechanism of action, and it is a task of vital importance to explore the signaling pathways of traditional Chinese medicines. Finally, although some active ingredients of traditional Chinese medicine have been proven to be able to delay the development of autoimmune hepatitis, such as tretinoin, their specific signaling mechanism is still unclear and needs further exploration. Therefore, it is necessary to dig more deeply into the specific targets and signaling pathways of the active ingredients of Chinese medicines, providing a theoretical basis for the application of it, so as to develop safer and more effective drugs for the treatment of autoimmune hepatitis.

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