

Progress of research on tetrahydrocurcumin against liver injury

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Author contributions

Ke-Yu Chen was responsible for drafting and revising the first draft; Jian-Bo Wang was responsible for reviewing and supervision; Shuang Luo was responsible for providing resources; Xue Wang and Yun-Teng Liu were responsible for project.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

THC, Tetrahydrocurcumin; ROS, Reactive oxygen radicals; SOD, Superoxide dismutase; GSH-Px, Glutathione peroxidase; MDA, Malondialdehyde; NAFLD, Nonalcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; ALD, Alcoholic liver disease; DILI, Drug induced liver injury.

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Abstract

Liver injury has become a serious liver disease worldwide, and its incidence is increasing year by year, bringing a serious health burden to people in all countries. Tetrahydrocurcumin is an active metabolite of curcumin, which has pharmacological effects such as antioxidant, anti-inflammatory, inhibition of apoptosis, anti-tumor, and anti-aging, and it can inhibit apoptosis in liver cells under the state of hepatic injury and reduce the level of oxidative stress and inflammation in liver tissues through the signaling pathways such as MAPK, PI3K/Akt, PPAR, AMPK, and Nrf2 to prevent and control liver injury. The purpose of preventing and controlling liver injury can be achieved. The active structure, pharmacological effects and application of tetrahydrocurcumin in liver injury were summarized by reviewing domestic and international literature, with a view to providing reference for further research on tetrahydrocurcumin in the field of liver injury.

Keywords: tetrahydrocurcumin; active structure; pharmacological effects; liver injury

Background

Liver Injury is a reaction to liver cell damage and changes in the physiological structure of the liver caused by one or more reasons leading to liver failure, and as the disease continues to develop, it will lead to liver fibrosis, cirrhosis, hepatocellular carcinoma and other serious diseases [1]. Common types of liver injury include alcoholic liver injury (ALI), chemical liver injury (CLI), and drug-induced liver injury (DILI), with common lesions including hepatocellular degeneration and necrosis, inflammatory cell infiltration, steatosis, and the presence of fibrous tissue [2, 3]. The incidence of liver injury has been increasing in recent years, and according to the World Health Organization, DILI has risen to become the 5th leading cause of death globally, while Global Burden of Disease (GBD) data show that alcohol-related liver injury accounts for 27% of deaths due to cirrhosis and chronic liver disease [4, 5]. Since the intrinsic mechanisms of different factors inducing the occurrence of liver injury have not been systematically elucidated, and the mechanism of liver injury is complex, inflammation, oxidative stress, apoptosis and necrosis are the common results of different types of liver injury, which involves multi-targets and multi-pathways acting together upstream [6]. Therefore, based on the complex pathogenesis and high incidence of liver injury, elucidating new pathways and their synergistic effects and finding new therapeutic agents suitable for various types of liver injury is an urgent problem.

Tetrahydrocurcumin (THC), the active metabolite of curcumin, was first detected in rat bile and metabolites by Holder et al. , and is derived from curcumin in vitro and in vivo by hydrogenation reduction or naturally occurring in the plants *Zingiber mioga*, *Z. officinale* and *Curcuma zedoaria* in their rhizomes, see Figure 1 [7–11]. Modern pharmacological studies have shown that THC can exert antioxidant, anti-inflammatory and apoptosis inhibiting effects through multi-targets and multi-pathways, and has been effective in preventing and controlling liver injury. The active structure, pharmacological effects and application of THC in liver injury are now reviewed, with a view to providing references for the subsequent in-depth studies.

Active structure of tetrahydrocurcumin against liver injury

An imbalance between reactive oxygen radicals (ROS) and antioxidant capacity in the liver then causes oxidative stress in the liver, ethanol and some drugs cause elevated ROS in the liver leading to liver injury, and alleviating oxidative stress is one of the strategies to ameliorate

liver injury [12]. The β -diketone part of the THC structure shows antioxidant activity by breaking the C-C bond at the active methylene carbon between the two carbonyl groups [13]. During the metabolism of curcumin to form THC in vivo, the conjugated double chain at the center of the structure is hydrogenated, which significantly enhances the antioxidant activity of THC [14]. Trivedi et al. used NMR to analyze THC in solution and found for the first time that THC exists in three reciprocal isomeric structural forms in solution depending on retention time: one keto and two enol forms, see Figure 2 [15]. Further comprehensive characterization of THC using liquid-mass spectrometry, gas chromatography, and spectroscopy revealed that curcumin exists as a keto-enol form in both solids and liquids. The enol form is the stable form of THC. This suggests that the change in the form in which THC exists may be one of the reasons for the change in its antioxidant activity.

Pharmacologic effects of tetrahydrocurcumin in the prevention of liver injury

Antioxidant

In metabolic liver injury, hepatic lipid accumulation due to disturbed lipid metabolism affects different ROS generators, including mitochondria and endoplasmic reticulum, which disturb the balance of hepatic oxidative and antioxidant capacity [16]. The antioxidant capacity of THC, on the other hand, is manifested in its ability to inhibit ROS production in vivo and increase the expression of two key enzymes for scavenging oxygen radicals, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), as well as to inhibit the production of malondialdehyde (MDA), an indicator of oxidative stress, which is an advantageous factor in mitigating the effects of oxidative stress on the liver. Li et al. found in in vitro and in vivo experiments that THC could exert antioxidant capacity by significantly inhibiting diabetes-induced ROS elevation through silencing information regulatory factor 1 (SIRT1) antioxidant pathway [17]. The mechanism is that THC reverses the diabetes-induced decrease in SIRT1 expression, reduces Ac-SOD2 expression and enhances SOD2 deacetylation to reduce ROS generation, and ultimately strengthens its own antioxidant capacity by repairing the activities of SOD and GSH-Px, and by decreasing the generation of MDA. In addition, THC enhances the expression of antioxidant proteins, including nuclear factor-redness-related factor 2 (Nrf2) and NAD (P) H phenyl diphenol oxidoreductase 1 (NQO1), and reduces the accumulation of ROS in the body [18]. Lipid peroxidation, which results from the interaction of ROS with lipids, is another manifestation of oxidative stress. Chaniad et al. compared the effects of curcumin and its derivatives on LDL

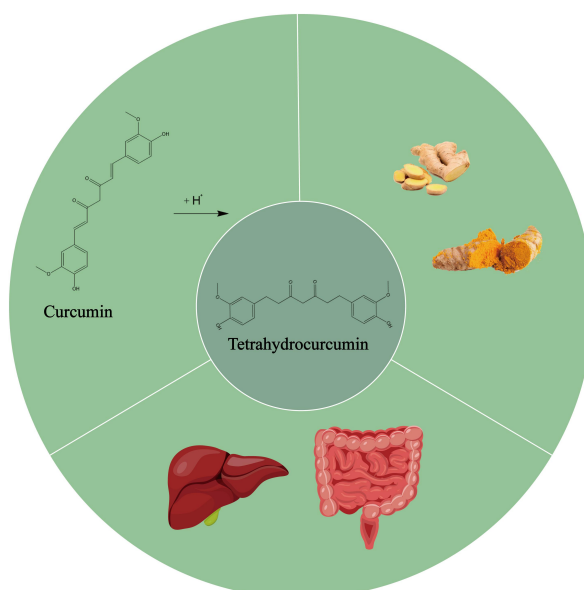


Figure 1 Source pathway of tetrahydrocurcumin

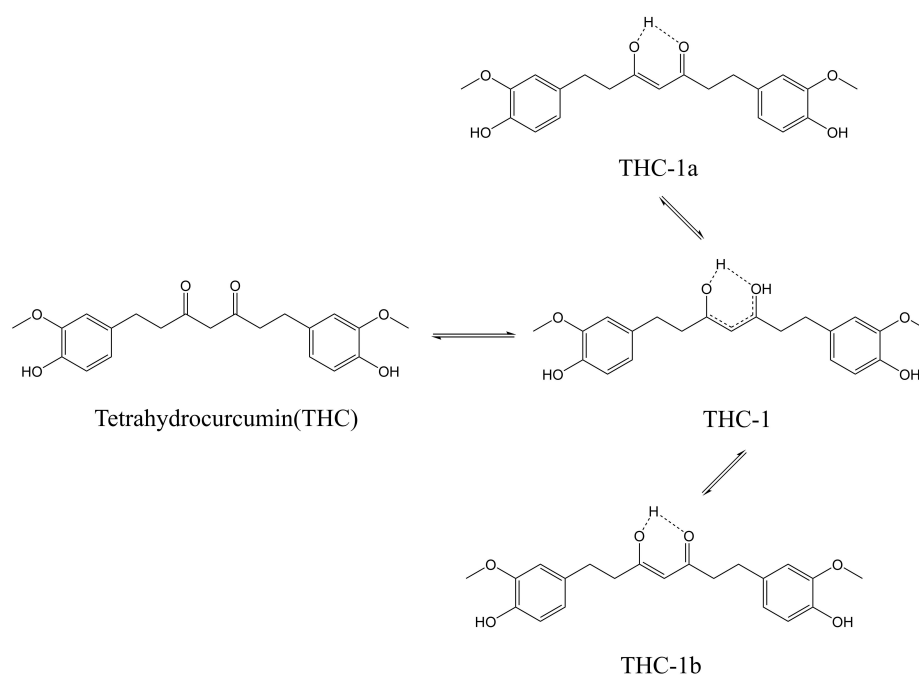


Figure 2 Structure of tetrahydrocurcumin

oxidation, and the effects on lipids and free radicals among the tested compounds were $\text{THC} \geq \text{curcumin} \geq \text{curcumin analogs} > \text{demethoxycurcumin} \geq \text{bisdemethoxycurcumin} \geq \text{vitamin E}$ [19]. The results suggest that THC has a better antioxidant activity and it may be through the attenuation of lipid peroxidation and reduction of the lipid oxidation induced increase in free radicals.

Anticancer

In metabolic stress liver injury, NAFLD patients may show different degrees of lymphocyte subpopulation disorders, and the imbalance of interleukin IL-10/IL-17 ratio promotes the inflammatory response of hepatocytes, which leads to further aggravation of liver injury, and the reduction of inflammatory response is one of the directions of the treatment to improve liver injury [20]. Mechanistic studies have shown that THC can effectively inhibit the production of pro-inflammatory and inflammatory factors in the inflammatory response through the mitogen-activated protein kinase phosphatase (MAPK) signaling pathway and the nuclear factor- κ B (NF- κ B) signaling pathway. The specific mechanism is that THC inhibits the release of tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 by up-regulating mitogen-activated protein kinase phosphatase 1 and preventing the phosphorylation of c-Jun N-terminal kinase (JNK) and extracellular signal-regulated protein kinase (ERK) [18]. The NF- κ B signaling pathway is a classical inflammatory pathway, and THC effectively alleviates the inflammatory response by regulating NF- κ B and thus affecting the expression levels of downstream targets such as TNF- α and IL-1 β [21]. THC was used to intervene with lipopolysaccharide to stimulate oxidative stress and inflammatory responses in RAW264.7 macrophages, in the experiment, THC was found to significantly inhibit the production and activation of NO, NF- κ B, and reduce the phosphorylation of MAPK and ERK, suggesting that THC may play a beneficial role in inflammatory responses through the NF- κ B/MAPK pathway, in particular, in the present experiment THC exhibited stronger anti-inflammatory activity than curcumin [22]. Koh et al. identified the metabolite 3-amino-3-deoxytetrahydrocurcumin (THC-NH2) in the feces of mice administered with THC, which possessed stronger anti-inflammatory activity than the former [23]. In the presence of THC-NH2, the protein expression level of nitric oxide synthase (iNOS) was significantly reduced, exerting a significant anti-inflammatory response in terms of nitrite production, but not increasing the level of prostaglandin E2.

Inhibition of apoptosis

Apoptosis is an active mode of programmed cell death, and excessive apoptosis of liver tissue cells is an important factor in the development of liver injury, experiments have found that drug-induced activation of hepatic apoptotic pathway, necrotic apoptosis, autophagy, and cellular pyroptosis are common modalities of drug-induced liver injury, and inhibition of apoptosis of hepatocytes can help to ameliorate the liver injury [24, 25]. Chen et al. found that THC effectively reduced the expression of apoptosis-related proteins (such as B-cell lymphoma (Bcl)-associated X protein (Bax), cysteine protease-3 (caspase-3)) and elevated the expression of Bcl-2 proteins, reversed the decrease in phosphorylation induced by hypoxia/reoxygenation of phosphoinositide 3-kinase (PI3K), threonine protein kinase (Akt), and mammalian target of rapamycin (mTOR), and induced the decrease in phosphorylation of hypoxia inducible factor-1 α (HIF-1 α) [26]. protein kinase (Akt), and mammalian target of rapamycin (mTOR) phosphorylation caused by hypoxia/reoxygenation, induced the expression of hypoxia-inducible factor-1 α (HIF-1 α), and effectively prevented cardiomyocyte apoptosis based on the PI3K/AKT/mTOR pathway. In addition to this, THC inhibits cell cycle arrest and apoptosis in microglia through the Ras/ERK signaling pathway, and in a mouse model of Alzheimer's disease, THC up-regulates the expression of transforming growth factor β 1 (TGF- β 1) and Bag1, and attenuates the aberrant expression of Gab2, Ccnd2, K-Ras, poly(ADP-ribose) polymerase 1 (PARP1), caspase-3, and TNF- α , of which Bag1 is a multifunctional anti-apoptotic protein, and Gab2 and Ccnd2 are associated with abnormal cell proliferation [27]. THC effectively restored glutamate-induced neuronal apoptosis. Chromatin condensation is a morphological feature of apoptosis, and THC effectively prevented glutamate-induced chromatin condensation in HT22 cells, which was found to be significantly reduced by glutamate-induced apoptosis in HT22 cells under the observation of propidium iodide (PI) and membrane-associated protein V (Annexin V) staining [28].

Tetrahydrocurcumin in liver injury

Non-alcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a type of metabolic stress liver injury that includes simple non-alcoholic fatty liver (NAFL), which develops as a result of excessive accumulation of fat, and

non-alcoholic steatohepatitis (NASH), which is characterized by inflammation of the portal vein and lobules as well as damage to hepatocytes [29, 30]. In one study, Gao et al. found experimentally that THC could prevent NAFLD by improving lipid metabolism and redox homeostasis [31]. THC reduced the expression of fibroblast growth factor 21 (FGF21) and elevated the mRNA levels of cytochrome 450 51 (CYP51) and FOXQ1 in the livers of NAFLD mice thereby regulating glucose-lipid metabolism and oxidative stress in mice. In cellular experiments, after THC intervention on HepG2 cells treated with OA, the expression of intracellular NRF2 and target genes NQO1, GSTA1, GCLM, and GCLC all increased with increasing THC dose, and THC significantly increased the expression of FGF21 mRNA in HepG2 cells. In this study, THC ameliorated the pathology of weight gain, elevated lipids and blood glucose, and hepatic steatosis induced by a high-fat diet. Interestingly, THC did not affect or decrease the body weight of NAFLD mice without affecting or increasing their food intake, a phenomenon that may be related to the stimulation of FGF21 by THC. FGF21 does not affect food intake, but it significantly increases energy expenditure in response to specific stimuli leading to the absence of body weight gain, and in addition to this, it may be related to the fact that FGF21 has anti-obesity properties Related [32, 33]. FGF21 has the physiological function of maintaining energy homeostasis, THC reduces peripheral insulin resistance by stimulating the expression of FGF21, reduces the substrate flux of adipogenesis and gluconeogenesis, and indirectly affects hepatic glucose and lipid metabolism to achieve the effect of improving NAFLD [34, 35]. In another cellular experiment, Chen et al. used different concentrations of THC to treat NAFLD cell models using oleic acid (OA)-induced NAFLD [36]. THC was found to reduce lipid accumulation in HepG2 cells by inhibiting the expression of lipogenic proteins, sterol regulatory element-binding protein 1 (SREBP-1c), peroxisome proliferator-activated receptor γ (PPAR γ), fatty acid synthase (FAS), and fatty acid-binding protein 4 (FABP4), and, in addition, THC in an adenosine monophosphate-activated protein kinase (AMPK)-dependent manner attenuated OA-induced hepatic lipogenesis, and in terms of glucose uptake and insulin resistance, THC restored glucose uptake and insulin signaling in HepG2 cells cultured with OA via phosphorylation of insulin receptor substrate 1 (IRS-1)/PI3K/Akt and downstream signaling pathways, FOXO1 and glycogen synthase 3 β (GSK3 β). The results of this experiment elucidated the mechanism by which THC ameliorates hepatic steatosis and demonstrated that THC is beneficial for improving NAFLD by reducing lipogenesis and accumulation and enhancing insulin signaling. In the latest research experiment, Wu et al. found that curcumin could improve hepatic lipid accumulation, inflammation and endothelial dysfunction in NASH rats through NF- κ B and PI3K/Akt/HIF-1 α pathways through in vivo and in vitro experiments, and this process was closely related to the conversion of curcumin to THC, and demonstrated that the THC improved the endothelial dysfunction in NASH in in vitro experiments. The effect of THC was stronger than that of curcumin, and in-depth study found that THC could significantly increase NO level, inhibit ANGPT2 expression, reduce VCAM-1 and ICAM-1 mRNA level to restore endothelial function of LSECs, attenuate the elevation of nuclear pp65/histone H3, p-Akt/Akt and p-PI3K/PI3K ratio, and improve endothelial function of NASH cells through NF- κ B and PI3K/PI3K/ Akt signaling pathways [37]. Akt signaling pathways to improve liver condition in NASH rats.

Alcoholic liver injury

Alcoholic liver disease (ALD), also known as alcoholic liver disease, includes simple steatosis, alcoholic hepatitis (AH) and cirrhosis and superimposed hepatocellular carcinoma, with oxidative stress, inflammatory response, and apoptosis of hepatocytes as the main pathogenic mechanism [38, 39]. Fermented turmeric effectively inhibited the expression of CYP2E1 and SREBP-1c proteins, increased the level of PPAR- α , increased the expression of AMPK and CPT-1 and decreased the expression of ACC in alcoholic fatty liver mice, which decreased the synthesis of fatty acids and increased the oxidation of

fatty acids, respectively, and improved alcoholic fatty liver to a certain extent, which was analyzed by high-performance liquid chromatography (HPLC) in which the content of THC and caffeic acid was more than raw turmeric, suggesting that the increased content of THC may have played a certain role in the prevention of alcoholic fatty liver [40]. It is suggested that the increased content of THC may play a role in the prevention of alcoholic fatty liver. SREBP-1c is a major regulator of lipid homeostasis and PPAR- α is an important link in cholesterol production and metabolism, it has been experimentally demonstrated that THC acts on and significantly affects the expression of SREBP-1c protein and PPAR- α in NAFLD, and that an increase in the content of THC in fermented turmeric may be the key to the enhancement of the effects on SREBP-1c protein and PPAR- α , thereby ameliorating ALD to some degree [41, 42].

Drug induced liver injury

Drug induced liver injury (DILI) is a liver injury induced by various drugs, dietary supplements and even excipients. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common predisposing factor in cases of liver injury, producing varying degrees of liver injury in about 10% of patients at normal doses used [43]. Acetaminophen (APAP) is a widely used nonsteroidal anti-inflammatory drug with antipyretic and analgesic properties, usually used for fever and pain. Most of APAP (85%) is metabolized by the liver and excreted in urine and bile, but a small portion (15%) is metabolized by the CYP450 enzyme to produce the toxic N-acetyl-paraquatic acid imide (NAPQI) that causes liver damage [44]. Excessive use of APAP is prone to cause acute pharmacological liver injury and acute liver failure [45]. Luo et al. used APAP to induce the formation of hepatic injury in mice. After the intervention of THC the impaired hepatic function and hepatic antioxidant status of mice were restored, and the levels of lipid peroxidation markers were significantly reduced, which showed strong antioxidant and hepatoprotective effects [46]. In this experiment THC showed a dose-dependent enhancement of liver function and attenuation of the pathological changes of liver injury in the effective concentration range, restored the hepatic antioxidant capacity by increasing the levels of GSH, SOD, CAT, and T-AOC, significantly inhibited the activity and expression of CYP2E1, and dramatically enhanced the translation of Nrf2-targeted genes (GCLC, GCLM, NQO1, and HO-1) activity, THC ameliorated APAP-induced pharmacological liver injury by attenuating the level of hepatic oxidative stress. CYP2E1 is one of the major ROS producers in the liver and THC can reduce the production of ROS and free radicals by affecting the CYPs to decrease the level of oxidative stress and thus reduce the damage to the liver [47, 48]. Notably, THC showed better hepatoprotective effects than silymarin in ameliorating liver injury induced by erythromycin esters [49].

Toxic liver injury

In industrial production, there is a high probability that people are exposed to heavy metals (cadmium (Cd), arsenic (As), etc.) through occupational or environmental conditions, and the accumulation of heavy metals in the liver, kidney and other organs will cause a series of diseases after exceeding a certain threshold [50]. It has been verified in animal experiments that THC can effectively improve hepatotoxicity induced by Cd and As, the damaged liver function and liver antioxidant status were restored, and the levels of lipid peroxidation markers were significantly reduced, which showed strong antioxidant and hepatoprotective effects [51, 52].

Conclusion

Tetrahydrocurcumin has a wide range of pharmacological effects, see Figure 3, and has achievements in the research of liver, cardiovascular, brain and other organ-related diseases and tetrahydrocurcumin, which may be due to the fact that tetrahydrocurcumin is the active metabolite of curcumin, which is still suffering from the problems of poor aqueous solubility, low bioavailability, and so on. With the deepening of the research, the new

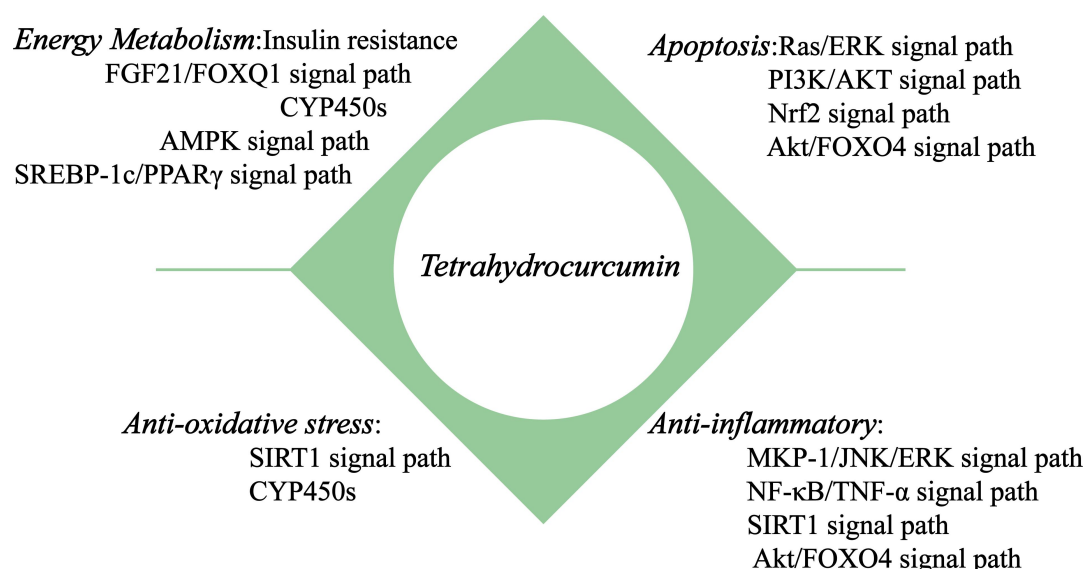


Figure 3 Mechanism of tetrahydrocurcumin action in liver injury

process method can effectively solve such problems and support the research of tetrahydrocurcumin in liver injury and other diseases and mechanisms, which makes tetrahydrocurcumin has a greater potential for development. Liver injury encompasses a wide range of diseases and its pathogenesis is complex, involving the influence of factors such as disorders of glucose and lipid metabolism, intestinal microorganisms, hepatic metabolic enzymes, and hepatic tissue fibrosis, in addition to physiological changes such as oxidative stress, inflammation, and apoptosis. At present, it has been reported at home and abroad that tetrahydrocurcumin is closely related to these physiological changes or pathways of action, which provides a reference and direction for further research on the mechanism of tetrahydrocurcumin to improve liver injury from multiple perspectives and aspects.

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