Acupuncture and Herbal Medicine

Dual effects of Psoraleae Fructus on the liver: hepatoprotection or hepatoxicity?

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Abstract

Psoraleae Fructus, the dried mature fruit of the leguminous plant *Psoralea corylifolia* L., contains flavonoids, coumarins, monoterpene phenols, and benzofurans. It exhibits various pharmacological activities, including immune regulation, antioxidant properties, photosensitivity, and estrogen-like effects, and finds extensive use in the clinical treatment of osteoporosis, vitiligo, and psoriasis. Extensive pharmacological research has demonstrated that Psoraleae Fructus and its components improve liver function and protect hepatocytes in animal and cellular models of liver diseases. Moreover, with the increasing clinical applications of Psoraleae Fructus and its derivatives, as well as the progression in adverse drug reaction surveillance, there is an increase in clinical cases involving these preparations and the enhancement of monitoring for any adverse reactions linked to Psoraleae Fructus and its related compounds. Here, we examined the hepatoprotective effects and hepatotoxicity of the monomer components, extracts, and related preparations of Psoraleae Fructus. We aim to contribute to safety evaluation, facilitate informed clinical application, and foster advancements in Psoraleae Fructus and its derivatives.

Keywords: DILI, Hepatic protection, Hepatotoxicity, *Psoralea corylifolia* L., Psoraleae Fructus

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Introduction

Psoraleae Fructus (Bu Gu Zhi, PF), termed "Buguzhi" in traditional Chinese medicine (TCM), is derived from dried mature fruit of the leguminous plant *Psoralea corylifolia* L. The earliest mention of PF dates back to an ancient Chinese medical book called *Lei's Treatise on Processing Drugs* (雷公炮炙论） Northern and Southern Dynasties, A.D. 420–581). It is characterized by its warm nature, pungent, and bitter taste, and its influence on the spleen and kidney meridians, where it significantly reinforces the kidneys to strengthen Yang, relieves chronic diarrhea and enriches the bone marrow.

To date, innumerable chemicals, including flavonoids, coumarins, monoterpene phenols, benzofurans, lipids, and volatile oils have been identified in PF. The primary active constituents are coumarins, flavonoids, and meroterpenes[1,2]. Based on the activity of its numerous chemical components, PF exhibits a range of pharmacological effects, including anti-inflammatory, antibacterial, antiviral, antioxidant, antitumor, photosensitizing, and estrogen-like effects, affecting various organs including brain[3–5], heart[6], lung[7], skin[2,8], and liver[9,10]. PF is utilized in a variety of preparations, including Zhuanggu Guanjie pill (ZGGJ), Xianling Gubao (XLGB) capsules, Fufang Buguzhi granule, and Buguzhi intramuscular injections, which, in combination with monomer components and PF extracts, are used to treat numerous diseases, including osteoporosis, osteomalacia, psoriasis and vitiligo, in the clinic[11–14].

With the widespread use of PF and its preparations, PF-induced multiple organ toxicity, including hepatotoxicity[15], nephrotoxicity[16,17], reproductive toxicity[17,18], and phototoxicity[12,19], have garnered widespread attention. The hepatotoxicity is the most common type and non-negligible challenge of multi-organ toxicity caused by PF and its preparations. The Chinese National Adverse Drug Reaction Monitoring Database received a total of 2,665 reports on XLGB oral preparations (January 1, 2004, to July 21, 2016), causing the Chinese Food and Drug Administration (CFDA) to issue a notification regarding the risk of liver injury associated with XLGB on December 8, 2016[20]. ZGGJ [National Center for ADR Monitoring, China, ADR notification (2008, No. 1)] and Baishi pills [National Center for ADR Monitoring, China, ADR notification (2008, No. 9)] have been reported to cause cholestatic liver damage. Additionally, a

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detailed exploration of the main active components in PF revealed their impact on various signaling pathways involved in liver dysfunction and disease, suggesting that PF and its preparations may exert hepatoprotective effects.

This paper reviews research progress on the hepatoprotective and hepatotoxic effects and the mechanisms, of the monomer components, extracts, and related preparations of PF, aiming to provide a comprehensive understanding of their effects on the liver.

Hepatoprotection

Alleviation of APAP-induced liver injury

Acetaminophen (APAP), widely used as an antipyretic and analgesic drug, stands as the primary cause of drug-induced liver injury (DILI)[21,22]. Various cellular processes, including phase I/II metabolism, mitochondrial oxidative stress (OS), endoplasmic reticulum (ER) stress, sterile inflammation, and autophagy, contribute to the pathogenesis of APAP-induced liver injury (AILI). N-acetyl cysteine (NAC), an effective clinical antidote for ameliorating AILI by scavenging reactive oxygen species (ROS), is constrained by its narrow therapeutic window. Therefore, identifying alternative approaches for treating AILI is imperative[23–25].

APAP undergoes oxidation primarily by cytochrome P450 (CYP450) enzymes, particularly CYP2E1, to form the reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI). This metabolite can be conjugated with hepatic reduced glutathione (GSH) for detoxification. When APAP overdose occurs, GSH is exhausted, thereby depleting NAPQI and initiating AILI. CYP enzymes present targets for protecting the liver against AILI. Furanocoumarins, a combination of coumarin and a furan ring, are among the major phytochemicals in PF interacts with the CYP450 enzyme system as a substrate, thereby inhibiting enzyme activity[26–29]. Administration of 25, 50, or 100 mg/kg Psoralen to C57BL/6J mice for five consecutive days (300 mg/kg APAP was administered on the fourth day) significantly ameliorated single-dose 300 mg/kg APAP-induced hepatic injury. Homology modeling and molecular docking predicted that the binding energy of Psoralen with CYP2E1 was E_f = –6.17, indicating the interaction was spontaneous. The results of the cocktail probe assay indicated that Psoralen inhibited the enzymatic activity of CYP2E1. In conclusion, Psoralen can act as a substrate of CYP2E1 to competitively bind to the active site of CYP2E1 with APAP, resulting in a disturbance in the enzymatic activity and rate at which CYP2E1 metabolizes APAP, thereby ameliorating AILI[10]. A single dose of 40, 80, or 120 mg/kg 8-methoxypsoralan (8-MOP) administered 1 hour after the administration of 300 mg/kg APAP significantly reduced aminotransferase levels and alleviated hepatic inflammation and damage. Molecular docking and cocktail probe assays demonstrated that 8-MOP exhibits a strong binding ability to CYP2E1 and modulates its enzyme activity, akin to Psoralen[30].

Further studies should be conducted to investigate whether other furanocoumarins or active components in PF can bind to CYP2E1 and influence its activity to provide an experimental foundation for utilizing PF and its preparations in the prevention and treatment of AILI.

Amelioration of hepatic steatosis and nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD), characterized by liver steatosis, is emerging as a prominent cause of cirrhosis and hepatocellular carcinoma (HCC) with increasing prevalence, contributing significantly to health and economic burdens[31–33].

Xiaoyao power (XYS), a well-known TCM prescription containing PF as the main active ingredient, has demonstrated remarkable therapeutic effects in alleviating corticosterone-induced (CORT) hepatic steatosis. Network pharmacology and protein expression in the liver have unveiled a close relationship between the glucocorticoid receptor (GR) and adipose differentiation-related protein (ADFP), highlighting their pivotal roles in the anti-steatosis effect of XYS. Similar to GR antagonists, XYS inhibits the increase in GR translocation and activation induced by a high-fat diet (HFD). Further investigation by overexpressing or knocking down GR in HepG2 cells revealed that GR, as the upstream of ADFP, positively regulates ADFP expression, suggesting that XYS ameliorates hepatic steatosis through the GR/ADFP signaling pathway[24]. Treatment of HFD-induced NAFLD mice with 300 or 500 mg/kg *Psoralea corylifolia* L. seed (PCS) extract for 12 weeks significantly reduced hepatic lipid accumulation, triglyceride levels, and inflammation, and improved plasma lipid profiles, indicating a significant ameliorative effect of PCS on NAFLD. The expression of genes involved in lipogenesis, including *sterol regulatory element binding protein (SREBP)-1c* and *stearoyl-coenzyme A desaturase (SCD) 1*, decreased, while the expression of proteins involved in lipid β-oxidation, including proliferator-activated receptor α coactivator (PGC1α) and carnitine palmitoyl transferase 1A (CPT1A), increased. These changes may contribute to the effects of PCS extract on hepatic lipid metabolism[34]. The same anti-steatosis effects were also observed in PF-treated juvenile mice with NASH, induced by HFD feeding in a maternal offspring manner[35]. Moreover, the mechanisms involved in OS[36], inflammation[33], and fibrosis[37] have been investigated because they are key factors in the progression of NASH. Results showed that PF inhibited the above pathologies through protein kinase C α (PKC-α)/nicotinamide adenine dinucleotide phosphate (NADPH), nuclear factor kappa-B (NF-κB), and phosphatidylinositide 3-kinase (PI3K)-protein kinase B (Akt) signaling pathways[35]. To identify potent compounds in PF and validate the aforementioned signaling pathways, a mouse primary hepatocyte model was established with palmitic acid (PA) as the stimulator. Five main compounds in PF, namely, Psoralen, Isopsoralen, Neobavaisoflavone, Isobavachalcone, and Bakuchiol (BAK), demonstrated efficacy in reducing OS, lipid accumulation, hepatocyte damage and inhibiting the activation of the PKC-α/nicotinamide adenine dinucleotide phosphate oxidase (NOX) signaling pathway, mirroring the effects of PC *in vivo*. Among these five compounds, Psoralen has the greatest efficacy in

ameliorating lipid-induced hepatocyte injury and blocking the PKC-α/NOX pathway[38].

Multiple studies have investigated the anti-steatosis effects of other compounds in PF. Epidemiological and experimental evidence suggests a correlation between the vitamin D-vitamin D receptor (VD-VDR) axis and the development of NASH[39–41]. 8-MOP, a potential ligand of VDR[42], mitigates hepatic steatosis by suppressing insulin substrate-1 (IRS1) signaling and increasing insulin substrate-2 (IRS2) expression, thereby downregulating downstream *de novo* lipogenesis due to VD deficiency in Sprague-Dawley (SD) rats[43]. Wei et al.[44] demonstrated that Bavachin (BV) exhibited significant therapeutic benefits in both HFD-induced NAFLD mouse models and PA/oleic acid (PA/OA)-stimulated mouse primary hepatocytes and Huh cell models. Liver RNA-seq was employed to elucidate the underlying mechanisms, followed by real-time fluorescence quantitative PCR (qPCR) analysis to validate these mechanisms. The findings indicated a downregulation of genes associated with lipid synthesis, accumulation, and transport. Moreover, there was a decrease in the expression of OS- and autophagy-related genes, coupled with increased mitochondrial numbers and structural improvements. Collectively, BV mitigated HFD-induced liver injury by regulating hepatic OS, autophagy, and lipid metabolism[44].

In summary, PF and its preparations demonstrate promising anti-steatosis therapeutic efficacy and can ameliorate liver damage by engaging in various lipid metabolism processes and modulating the expression of genes in multiple signaling pathways. These findings highlight the potential of PF and its preparations for development as clinical drugs for the treatment of hepatic steatosis.

Inhibition of liver cancer

Liver cancer is a global health challenge associated with HCC is the most common form of it. Chronic hepatitis B and hepatitis C, metabolic liver diseases (particularly NAFLD), and exposure to toxins such as alcohol are key risk factors for HCC[45–47]. Although progress has been made in the treatment of HCC, there are still some issues with the implementation of effective treatment measures. Numerous studies have demonstrated the antitumor properties of TCM and their active monomers, indicating their therapeutic potential[48,49].

Considering that 8-MOP can induce apoptosis and has relatively low cytotoxicity in hepatoma HepG2 cells, with the value of half maximal inhibitory concentration (IC_{50}) are (124.07 ± 6.89) μM after 24 h of treatment, Xiong et al.[50] investigated the antitumor effect of 8-MOP. Cell adhesion, migration, and invasion were inhibited after 8-MOP treatment at concentrations ranging from 12.5 to 50 nM in HepG2 cells, which are much lower than the IC_{50} values. Additionally, they found that epithelial-mesenchymal transition (EMT)-related genes were modulated to lower levels. Moreover, 8-MOP suppressed the expression of differentiated embryonic chondrocyte-expressed gene 1 (DEC1) in a concentration-dependent manner, implicating its involvement in the regulation of the EMT process. Overexpression of DEC1 reversed the antimetastatic effects and decrease in EMT marker expression induced by 8-MOP in HepG2 cells, suggesting that DEC1 is a target of 8-MOP. Similarly, 8-MOP (5 or 20 mg/kg) suppressed lung metastasis in hepatoma H22-transplanted mice without causing multiple organ damage by downregulating DEC1 *in vivo*[50].

Several studies have demonstrated that Psoralen induces apoptosis by elevating the expression of the pro-apoptotic protein Bax, inhibiting the expression of the anti-apoptotic protein Bcl-2, upregulating the enzymatic activity of caspase-3[51] and triggering ER stress[52] in SMMC7721 hepatoma cells. Due to recent research which mentioned that SMMC7721 cells have been contaminated by Hela cells[53–55], specific antitumor mechanisms of Psoralen explored in these cells are not be elucidated here, but these results suggest that Psoralen may possess antitumor activity.

Currently, studies on the effects of PF and its preparations on the development and occurrence of liver cancer are limited. Further research is needed to determine whether PF can be developed as an anti-HCC drug, or whether it can synergistically enhance the antitumor activity of other antitumor drugs.

Hepatotoxicity

Mitochondrial dysfunction

Mitochondria are crucial organelles responsible for maintaining energy homeostasis and regulating cellular metabolism. Mitochondrial dysfunction inhibits fatty acid β-oxidation and increased OS, ultimately leading to cell apoptosis or death. This dysfunction has been shown to play a role in the occurrence and progression of various liver diseases[56–58].

XLGB is associated with a risk of DILI in clinical use. Experimental research showed that PF lowered the maximum respiratory capacity of HepG2 cells, as measured by the Seahorse assay, whereas the other five herbal medicines in XLGB had no impact on it. High performance liquid chromatography-time of flight/mass spectrometry (HPLC-TOF/MS) was used to characterize the five main compounds in PF: Psoralidin, Isobavachalcone, Bavachinin, BV, and Psoralen. These five compounds are the key factors in PF-induced mitochondrial dysfunction as they can suppress basal respiration, ATP-linked production, and maximal respiration to inhibit mitochondrial respiration. According to results of network pharmacology, the PI3K-AKT signaling pathway is closely related to abnormalities caused by XGBL[20]. Additionally, ethanol extracts of PF (EEEP) can significantly reduce the mitochondrial membrane potential (MMP) in L-02 and HepG2 cells, confirming that PF compounds can lead to mitochondrial dysfunction[59].

BV, the main flavonoid in *Psoralea corylifolia* L., induces mitochondrial damage *via* multiple mechanisms. Changes in the morphology of mitochondria in HepG2 cells, including the total area, width, height, length and breadth, were observed, and the MMP decreased significantly after exposure to 40 μM BV. Additionally, BV can downregulate the protein levels of mitofusion 2 (Mfn2), and the depletion of Mfn2 by siRNA exacerbates mitochondrial-induced ER stress and apoptosis[60].

BV (200 mg/kg) slightly upregulated aminotransferase levels, and caused mitochondria swollen, round-shaped and cristae disrupted in C57BL/6J mice. An imbalance between fission and fusion was evident, characterized as the expression of the pro-fission markers dynamic-related protein 1 (DRP1) and fission (FIS1) increased and the expression of pro-fusion markers Mfn2 and optic atrophy 1 (OPA1) decreased. RNA-seq analysis unveiled a closely association between hepatoxicity and the wingless/integrated (Wnt)/β-catenin signaling pathway, corroborated by the heightened expression of Wnt and β-catenin in BV-treated livers. Changes in the expression were observed in 20 μM BV-treated L-02 cells mirrored those in the liver. Treatment with XAV-939, a potent tankyrase inhibitor that targeting Wnt/β-catenin, and Mdivi-1, a mitochondrial fission inhibitor, alleviated mitochondrial dysfunction and reversed BV-induced hepatotoxicity in both L-02 cells and mice. Additionally, inhibition of Wnt/β-catenin by XAV-939 blocked mitochondrial fission and restored mitochondrial fusion, evidenced by decreased DRP1 and elevated OPA1 expression. Nevertheless, siDRP1 did not induce significant alterations in Wnt or β-catenin activation in L-02 cells, indicating that the Wnt/β-catenin is likely acts as an upstream signaling mechanism regulating DRP1 activity during BV-induced hepatocyte injury conditions[61].

In summary, multiple compounds in PF can affect the physiological function and state of mitochondria, resulting in mitochondria-associated hepatic damage. Thus, maintaining the mitochondria may be a potential way to intervene in the toxicity of PF and its preparations.

ER stress

The ER is a crucial intracellular organelle that plays a crucial role in maintaining cellular homeostasis by facilitating the correct folding of linear polypeptides and proteins. ER stress occurs when the failure to shape the proper three-dimensional architecture of proteins, culminating in the accumulation of misfolded or unfolded proteins within the ER, resulting in the disruption of ER homeostasis. In response to ER stress, the unfolded protein response (UPR) is activated to re-establish ER homeostasis or to induce cell death if ER stress persists[62–64]. Numerous studies have demonstrated the involvement of ER stress in various liver diseases[65–66].

Psoralen significantly activates the PERK-eIF2α-ATF4-CHOP and ATF6-CHOP ER stress signaling pathways, leading to ER stress-induced apoptosis in HepG2 cells, as evidenced by elevated expression of these proteins upon Psoralen treatment. Pretreatment of HepG2 cells with 4-phenylbutyrate (4-PBA) before Psoralen, an ER stress inhibitor, ameliorates apoptosis[67]. Similarly, BV also induces ER stress[60,68]. Yang et al.[68] discovered Sestrin2, a highly conserved stress-inducible protein involved in cellular responses to various stress conditions and homeostatic regulation, significantly increased ER stress-dependent hepatocyte damage. Knockdown Sestrin2 by siRNA dramatically aggravated BV-induced ER stress in HepG2 cells. Moreover, AMPK/mTORC1 acted downstream of Sestrin2 by both overexpression and inhibition of Sestrin2 can modulate this signaling pathway. These findings highlight Sestrin2 as a critical target that protects HepG2 cells against BV-induced ER stress, primarily by activating the AMPK/mTORC1 signaling pathway[68].

Cholestatic liver injury

DILI can manifest as hepatocellular, cholestatic, or mixed types. Drug-induced cholestasis (DIC) may present as bland cholestasis, cholestatic hepatitis, secondary sclerosing cholangitis, or vanishing bile duct syndrome[69–71]. DIC is a prevalent cause of DILI, with an associated mortality rate as high as 10%, imposing significant burden on clinical safety management and the pharmaceutical industry[72,73].

Exposure to EEEP at concentrations ranging from 1.80 to 2.25 g/kg led to a slight increase in serum aminotransferase levels in SD rats after 30 days of treatment. However, the expression of hepatobiliary injury markers, including alkaline phosphatase (ALP) and γ-glutamyl transferase (γ-GGT), was significantly elevated, particularly in female rats compared to male rats, indicating a higher sensitivity of female rats to EEEP-induced DIC[74,75]. Proteomic techniques based on isobaric tags for relative and absolute quantification (iTRAQ) combined with liquid chromatography-tandem mass spectrometry (LC-MS/MS) were used to identify, screen, and quantitatively analyze differentially expressed proteins (DEPs) to determine the crucial proteins and related signaling pathways implicated in EEEP-induced DIC. The results of biological function (gene ontology) and Kyoto encyclopedia of genes and genomes (KEGG) analyses revealed that bile secretion, the peroxisome proliferator-activated receptor (PPAR) signaling pathway, lipid metabolism, drug metabolism, and the CYP450 pathway were the main pathways involved in the response to EEFP-induced liver injury[75].

Administration of 8-MOP at concentrations ranging from 150 to 400 mg/kg, which is much lower than the half lethal dose (LD_{50} = 791 mg/kg), for 28 days markedly increased the levels of serum total bile acid (TBA), total bilirubin (TBIL), direct bilirubin (DBIL), and γ-GGT in female SD rats[42,76]. Hematoxylin-eosin staining and immunochemistry showed that the biliary epithelial cells (BECs) were injured. In the 8-MOP-treated group, the output of biliary phospholipids (PL) decreased and biliary secretion increased. A decrease in the PL/TBA ratio indicates higher bile toxicity. Accordingly, the PL regulators peroxisome PPARα and transporter multidrug resistance protein 3 (MDR3) were analyzed. The results demonstrated that 8-MOP inhibited the PPARα-MDR3 axis. *In vitro* experiments confirmed the inhibitory effects of 8-MOP on the PPARα-MDR3 axis in L-02 cells, suggesting that 8-MOP interferes with PPARα-MDR3-mediated PL efflux and bile acid homeostasis[76]. Psoralen (80 mg/kg), twice the maximum clinical intake dosage of psoralen, induced DIC to varying degrees in C57BL/6J mice after administration for 1, 3, and 7 d. LC-MS/MS, utilized to measure the hepatic bile acid profile after 14 d of Psoralen treatment, indicated an altered hepatic bile acid disorder characterized by an elevated total amount of bile acid and the accumulation of unconjugated bile acids. Psoralen downregulated bile acid transport, including that of the bile salt export pump (BSEP) and organic

solute transporter α (OSTα), and activated the key synthesis enzyme 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMGCR) contributed to the occurrence and progression of Psoralen-induced cholestatic liver injury[77]. BAK administered at doses of 52.5 and 262.6 mg/kg for 6 weeks can also induce DIC, leading to decreased expression of CYP7A1, HMG-CoA reductase, PPARα, and SREBP-2[78]. iTRAQ results confirmed the close association of PPARα, FXR, and CYP7A1 with the development and progression of BAK-induced cholestatic hepatoxicity[79].

In the 16th issue of *the Adverse Drug Reaction Information Bulletin*, the CFDA reported 158 cases of adverse reactions after using a Zhuangguguanjie pill, characterized by cholestatic liver injury. Additionally, research in animals and cells has indicated that PF affects multiple pathways involved in the synthesis, metabolism, and transport of bile acids. Therefore, owing to the alertness of clinical cases and experimental data, it is vital to consider the application of PF and its preparations to avoid DIC. Moreover, subsequent research should explore whether existing methods for the intervention and treatment of cholestatic diseases can be utilized to treat PF- and PF-induced cholestatic liver injuries.

Idiosyncratic hepatic injury

Idiosyncratic hepatotoxicity is caused by agents that have little or no intrinsic toxicity and cause liver injury in rare cases. Idiosyncratic drug-induced liver injury (IDILI) is mainly caused by two major factors: idiosyncratic metabolic and immunologic reaction[22,80,81]. Many TCM have been shown to induce idiosyncratic hepatic injury, including *Polygonum multiflorum* Thunb., which is the most well-known[82–84]. Two PF-containing TCM preparations, ZGGJ and XLGB, have been reported to cause liver injury with the characteristics of idiosyncratic hepatotoxicity induced by CFDA[85,86].

BV induced the highest increase in caspase-1 enzymatic activity compared to the other seven compounds (Angelicin, Isobavachin, Backuchiol, Psoralidin, Bavachinin, Neobavaisoflavone, and Psoralen) from PF in ATP- or nigericin-stimulated lipopolysaccharide (LPS)-primed BMDMs, suggesting that BV may promote inflammasome activation. Only the nigericin-induced NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome was activated, whereas other inflammasomes, including the NOD-like receptor family CARD domain containing 4 (NLRC4) and melanoma 2 (AIM2) inflammasomes, were not affected. In C57BL/6J mice, a single dose of 25 mg BV or 2 mg/kg LPS did not induce hepatic damage, but the combined administration (BV was administered 2 hours after LPS administration) caused IDILI. MCC950, an NLPR3 inhibitor, can reverse injury[87]. Wang et al.[88] demonstrated that 50 mg/kg Psoralidin could also cause IDILI after co-treatment with 2 mg/kg LPS. In addition. Psoralidin can activate not only the NLRP3 inflammasome but also the NLRC4 inflammasome, as using MCC850 in LPS-primed BMDM or conducting experiments in BMDM isolated from Nlrp3$^{-/-}$ mice failed to suppress the activation of inflammasome completely. The MitoSOX Red mitochondrial superoxide indicator assay revealed that the production of mitochondrial reactive oxygen species (mtROS) and NAC, a ROS scavenger, dramatically inhibited inflammasome activation and jointly uncovered mtROS as a decisive upstream mechanism of Psoralidin-induced NLRP3 and NLRC4 inflammasome activation[88].

Although the prevalence of IDILI is low, it can cause severe liver damage and irreversible acute liver failure. At present, IDILI induced by PF and its preparations has been reported; therefore, it is urgent to identify which compounds have the risk of inducing idiosyncratic hepatotoxicity and to elucidate the mechanisms involved, providing a theoretical basis for rational clinical drug use.

Conclusion

In summary, the hepatoprotective effects of PF and its preparations include alleviating AILI, ameliorating hepatic steatosis and NAFLD, promoting the apoptosis of HCC cells, and inhibiting their migration. In hepatotoxicity, PF and its preparations damage the mitochondria, induce ER stress in hepatocytes, disrupt hepatic bile acid homeostasis, and induce IDILI (Figure 1).

Based on the existing research, due to its complex active components with numerous effective targets, and complexity of compatibility with other TCM, the dominant signaling pathways may vary under different body states, drug dosages, and formulation selection, ultimately cause PF to play different effects on the liver.

Studies on the liver protection and hepatotoxicity of monomer components, extracts, and preparations of PF and formulations containing PF combined with other TCM are limited and not yet comprehensive. The numerous active ingredients in PF enable it to be developed to improve hepatic dysfunction and treat liver diseases. With the continuous development of system biology technologies, subsequent research can use these techniques to predict potential therapeutic targets and pharmacological effects and explore whether they can alleviate liver disease damage. Thus, the hepatotoxicity of PF and its preparations should be carefully considered. Current research on PF and its preparation-related hepatotoxicity has mostly been conducted in cells and animals in a physiological state, which is inconsistent with the clinical medication situation, resulting in difficulties in fully reflecting PF toxicity. Accordingly, cellular and animal disease models should be established to explore the hepatic effects of PF and its preparations under pathological conditions.

Taken together, in-depth investigations of the hepatoprotective and hepatotoxicity mechanisms of the monomer components, extracts, and preparations of PF are beneficial for developing drugs or new indications. This contributes to rational clinical use and maximizes therapeutic effects without inducing hepatic injury.

Conflict of interest statement

The authors declare no conflict of interest.

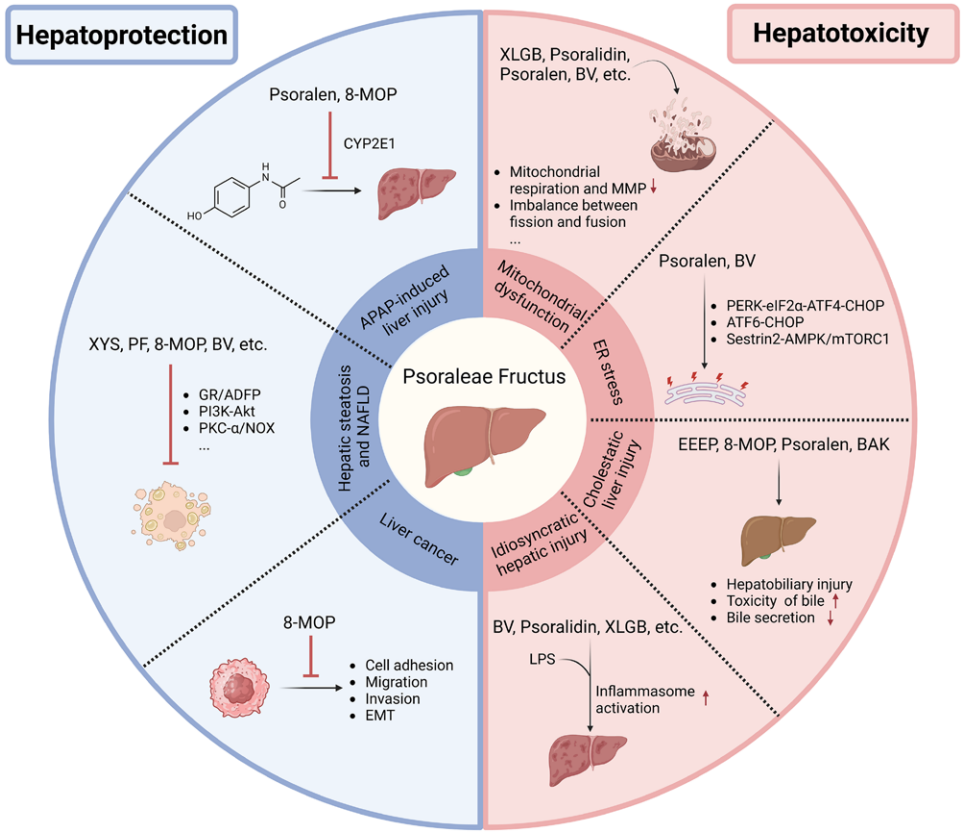

Figure 1. Schematic diagram illustrating the dual effects of Psoraleae Fructus on the liver (created by Scientific Image and Illustration Software | BioRender). 8-MOP: 8-Methoxypsoralan; BAK: Bakuchiol; BV: Bavachin; EEEP: ethanol extracts of PF; EMT: epithelial-mesenchymal transition; PF: Psoraleae Fructus; XLGB: Xianling Gubao capsules; XYS: Xiaoyao Power.

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Author contributions

Conceptualization: Qianhui Tang, Zhenzhou Jiang, and Luyong Zhang; writing-original draft preparation: Qianhui Tang and Zhenzhou Jiang; writing-review and editing: Qinwei Yu, Bin Ni, Zhenzhou Jiang, and Luyong Zhang. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

All data generated or analyzed during this study are included in this published article.

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