Available online at www.sciencedirect.com
ScienceDirect
Chinese Journal of Natural Medicines 2022, **20**(11): 805-813
doi: 10.1016/S1875-5364(22)60234-6
Chinese Journal of Natural Medicines

•Review•

A systematic review on the safety of Psoraleae Fructus: potential risks, toxic characteristics, underlying mechanisms and detoxification methods

SHI Zhuo, GAO Jing, PAN Jinchao, ZHANG Zuqi, ZHANG Guangchen, WANG Yuguang*, GAO Yue*

Department of Pharmaceutical Sciences, Beijing Institute of Radiation Medicine, Beijing 100850, China

Available online 20 Nov., 2022

[ABSTRACT] Psoraleae Fructus (PF) is an important traditional herbal medicine with a long history of clinical application. It is widely used to treat various diseases, such as osteoporosis, leucoderma and diarrhea. As a traditional nontoxic herb, it has aroused worldwide concern about the potential risks due to increasing adverse reaction events. This article reviews the botany, ancient records of medical uses, adverse reactions, toxicological research advance and detoxification methods of PF. According to clinical studies, liver injury is the most predominant in PF-related adverse reactions. The underlying mechanisms include bile acid metabolism and transport disorders, oxidative stress, mitochondrial damage, inhibition of liver cell regeneration and inflammatory reactions. Furthermore, the potential toxins of PF are summarized. Traditional methods of processing and compatibility will provide reference for reducing the toxicity of PF, which requires further research. In sum, this work systematically summarizes the reserach progress on the safety of PF, which will provide comprehensive insights into the toxicity of PF and facilitate its safe use and future development.

[KEY WORDS] Psoraleae Fructus; Toxic characteristics; Detoxification compatibility; Toxic substances; Hepatotoxicity; *Psoralea corylifolia* L.

[CLC Number] R965 **[Document code]** A **[Article ID]** 2095-6975(2022)11-0805-09

Introduction

Herbal remedies are increasingly popular around the world in the past decades. Depite the promising efficacy of a large number of herbal products, more frequent adverse events have been seen, which pose great challenges in safe use. As a representative nontoxic medicine, Psoraleae Fructus (PF, the dried fruits of *Psoralea corylifolia* L.) is widely used in many countries to treat osteoporosis, leucoderma, diarrhea and cardiovascular diseases, and currently not included in the list of toxic herbs in *Chinese Pharmacopoeia* [1]. However, recent attention has been drawn upon some liver injury reports of PF [2, 3]. A large volume of studies were performed to evaluate the toxicity of PF and its compositions, but less systematic study has been done on their toxicity and potential mechanism of action. This paper was designed to comprehensively summarize the adverse reactions, potential toxicity, molecular mechanisms, and detoxification methods of PF in an effort to facilitate its safe use and promote drug development.

Botany

Psoralea is a large widely distributed genus of herbs throughout tropical and subtropical regions, in which *Psoralea corylifolia* L. has long been used in traditional Chinese and Ayurvedic medicine. From ancient times to the present, there are countless descriptions about its appearance in herbal books. *P. corylifolia* L. is an annual upright herb, with a height of 60−150 cm (Fig. 1A). The branches are hard, fully covered with white villi. The leaf blade is broadly ovate with black glandular spots on both sides, and sparsely hairy or nearly glabrous. The pericarp is black and its surface is irregular reticulate. Its dried ripe fruits, Psoraleae Fructus (Bu Gu Zhi in Chinese) are flat and fragrant (Fig. 1B). The whole plant has crucial medicinal properties for the treatment of various diseases, such as leukoderma, menstruation disorder, uterine hemorrhage and lumbago. PF and its pharmaceutical preparations are also widely used to treat bone and skin diseases in China. The main constituents dominate its bioactivities, such as antitumor, anti-inflammatory, anti-oxidant, and osteoblastic effects (Table 1).

[Received on] 02-Apr.-2022
[Research funding] This work was supported by the Major Program of National Natural Science Foundation of China (Nos. 82192910 and 82192911).
[*Corresponding author] E-mails: wangyg@bmi.ac.cn (WANG Yuguang); gaoyue@bmi.ac.cn (GAO Yue)
These authors have no conflict of interest to declare.

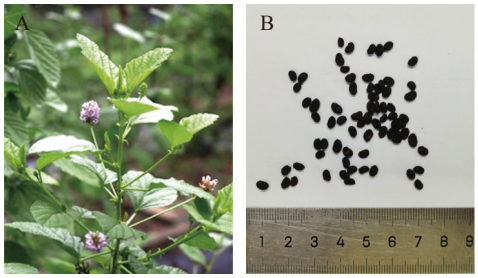

Fig. 1 Aerial part (A) and dried ripe fruit (B) of *Psoralea corylifolia* Linn. (A) is obtained from the Plant Photo Bank of China (http://ppbc.iplant.cn/)

Ancient Records of PF

The earliest record of PF appeared in a Chinese medical book called *Lei's Treatise on Processing of Drugs* (Lei Gong Pao Zhi Lun), where its characteristics and medical use were described in detail. It exerted significant effect of reinforcing the kidneys (Bu Shen) to strengthening Yang (Zhuang Yang), relieving chronic diarrhea and enriching the bone marrow. Additionally, PF has fierce property; it should be first soaked in liquor overnight, followed by rinsing with water for three days, before it is steamed for eight hours, and dried under the sun for later use. These descriptions indicated that the potential toxicity of PF had been observed by ancient people, and the processing methods such as alcohol soaking and water rinsing can reduce the toxicity.

In TCM theories, medicines are potions and poisons with both efficacy and adverse effects. Balancing patient conditions with the potential risks of drugs to be used, Chinese physicians prescribe reasonable dosage with proper compatibility to ensure the efficacy and eliminate harmful effects. Due to the different characteristics of herbs, it is essential to take advantage of their common efficacy and reduce adverse effects. In some medical books, it was mentioned that PF had the property of dryness (Zao). It was clearly represented in *Newly Revised Materia Medica* (Xin Xiu Ben Cao) that the compatibility of PF and Juglandis Semen prevented the dryness of PF. There were many similar descriptions, for instance PF was rarely used alone, but used in combination with one or two herbs of nourishing Yin. It implied that the current adverse reactions of PF may be related to its dryness.

Adverse Reactions and Clinical Characteristics

In recent years, some PF-related adverse reactions have been reported, such as hepatotoxicity, phototoxic dermatitis and allergy, where liver injury is the most frequent. TIAN *et al.* systematically analyzed 84 cases of PF adverse reactions raning from 1978 to 2016 [25]. A total of 48 patients were dignosed with liver injury, accounting for 57.14% of all cases. Other clinical studies also indicated the high hepatotoxicity risk of PF. ZHU *et al.* evaluated 595 inpatients with herb-induced liver injury (HILI) and found that 40 prescriptions contained PF in their medical history [26]. The clinical characteristics of PF-induced hepatotoxicity include patients older than 40 years of age, a higher proportion of women and mixed pattern of liver injury (hepatocellular and cholestatic types) [27-29]. The median number of days from medication to liver injury was about 29 days, and the oral dose was 2.4−4.8 g per day, with the cumulative dose ranging from 3.6−699.6 g. Furthermore, 96.7% of patients recovered after treatment or drug withdrawal. Some factors may increase the risk of liver injury, such as overdosing, taking the raw product, and improper compatibility of PF.

Advances in Toxicological Studies

PF has potential risks in some toxicological studies, inducing liver and kidney injury, reproductive toxicity and photosensitivity toxicity. The hepatotoxicity of PF is a non-negligible challenge with some controversial questions to be solved. Clinical cases of renal or reproductive injury induced by PF are rarely seen, but it is neceeary to closely observe

Table 1 The bioactivities and related representative compounds of *Psoralea corylifolia* L

No.	Bioactivities	Representative compounds	Reference
1	Anticancer	Psoralen, isopsoralen and psoralidin	[4-7]
2	Osteoblastic effct	Psoralen, bavachin, isobavachin,corylin and bakuchiol	[8-10]
3	Anti-oxidation	Psoralen, isopsoralen, psoralidin, bavachinin, isobavachin, corylifol A, isobavachalcone, and bakuchiol	[11, 12]
4	Anti-inflammation	Isopsoralen, psoralidin, bavachin, bavachinin, corylin, corylifol A, bavachalcone, isobavachalcone, and bakuchiol	[13-15]
5	Antimicrobial effect	Psoralen, isopsoralen, psoralidin, bavachin, bavachinin, bavachalcone, isobavachalcone, corylifol B, and bakuchiol	[16, 17]
6	Estrogenic effect	Psoralen, isopsoralen, psoralidin, bavachin, corylifol A, isobavachalcone, and bakuchiol	[18, 19]
7	Antidepression	Psoralen, isopsoralen, and psoralidin	[20, 21]
8	Improving aging-related diseases	Bavachin and bavachinin, bavachalcone and isobavachalcone	[22]
9	Neuroprotection	Bavachin and bavachinin, bavachalcone and isobavachalcone	[23]
10	Improving cardiovascular function	Bakuchicin	[24]

medication response to avoid possible risks. The toxicological research progress of PF is summarized in order to provide a breakthrough in understanding the questions.

Hepatotoxicity

Over the past decade, liver injury induced by PF has been extensively investigated in rats, mice and zebrafish. Taking an overdose or long-term of PF may lead to obvious hepatotoxicity [30, 31]. Complex mechanisms pose a great challenge to resolve the hepatotoxicity induced by PF. There is still controversy about the type of liver injury induced by PF, for example instinct or idiosyncratic hepatotoxicity. WANG *et al.* evaluated the effects of the ethanol extract of PF in rats for 28 consecutive days and results demonstrated hepatic cholestasis and instinct liver injury [32]. DUAN *et al.* utilized quantitative proteomics and metabolomics analysis and found that the alteration of bile acid metabolism was highly associated with liver injury induced by PF [33]. However, some studies suggested that PF and its preparation (Zhuanggu Guanjie Pills) induced T lymphocyte recruitment to the liver on low-dose lipopolysaccharide mediated rats, which may result in idiosyncratic liver injury. ALT and AST significantly increased, several cytokines were over-expressed and an intense inflammatory response was activated in rats. Further metabonomics analysis showed that sphingolipid metabolism and tyrosine metabolism were seriously altered in rats, which partly reflected the mechanism of liver injury [34, 35]. Furthermore, WU *et al.* found that the compatibility of PF and Paeoniae Radix Rubra attenuated the idiosyncratic hepatotoxicity induced by PF through regulating the arachidonic acid and glycerol phospholipid pathways [36].

Some efforts have been dedicated to the hepatotoxicity mechanism of PF, which involves bile acid metabolism and transport disorders, oxidative stress, mitochondrial damage, inhibiting liver cell regeneration and repair, and inflammatory reaction (Fig. 2). Bile acid accumulation and hepatocyte apoptosis are the research hub. Coumarins in PF are involved in multiple pathways, and flavonoids induce endoplasmic reticulum stress and interfere with metabolic detoxification. Monoterpene phenols play a role in bile acid transporters. The upstream molecules induced by coumarins include the recombinant farnesoid X receptor (FXR) and protein kinase R-like ER kinase (PERK). However, it remains unclear which factors are the exact triggers of PF-induced liver injury. Systematical and rigorous studies will clearly reveal the onset events and toxic molecules in the process in the near future.

Nephrotoxicity

Some studies suggested that administration of PF for 21 days led to kidney injury in mice [37]. The histological changes were characterized by enlarged endothelial cells and interstitial nuclei in the capillary plexus and turbidized epithelial cells of the proximal convoluted ducts. Pharmacokinetics research revealed that the CYP450 enzyme was inhibited and the exposure of bakuchiol increased after PF treatment [38]. Besides, psoralen was proven to induce the apoptosis of Hhuman kidney-2 (HK-2) cells [39].

Reproductive toxicity

WANG *et al.* found that PF extract reduced the mRNA expression related to steroid hormone production in the adrenal glands and inhibited androgen secretion, leading to damages in the prostate, seminal vesicle and adrenal gland in

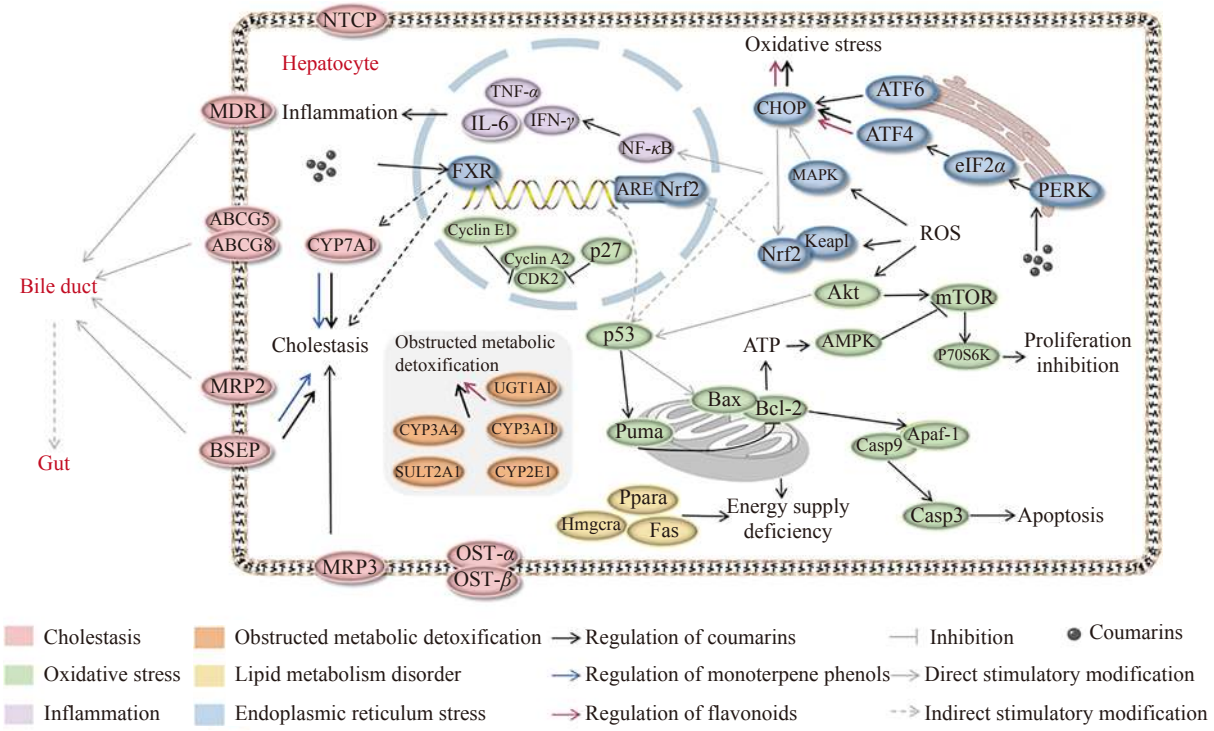

Fig. 2 Hepatotoxicity mechanisms of PF and its main components

rats [40]. Diawara *et al.* found that long-term administration of PF resulted in weak ovarian function, and decreases in ovulation number, estrogen level and uterine quality in female mice [41].

Phototoxicity

The phototoxicity mechanism of PF has been clarified, which is related to the photochemical reaction of a few coumarins, such as psoralen and 8-methoxypsoralen. Contact or oral administration made these photosensitive components distributed in skin tissues, which then significantly increased ultraviolet absorption (250−320 nm), stored energy and produced energy transfer, leading to skin toxicity with erythema epidermis [42, 43].

Potential Toxic Compounds

More than 200 compounds were isolated and identified from PF, including coumarins, flavones, meroterpenes, lipids, and volatile oil [44, 45]. Many constituents and metabolites have significant bioactivities, but some of them demonstrate potential toxicity. These potential toxic compounds have been explored from different perspectives. In the study, they are categorized based on their chemical structures and their toxic characteristics are summarized in Table 2.

Coumarins

Jois *et al.* isolated and identified psoralen and isopsoralen from PF, which are considered as two main active components of PF [60, 61]. According to *Chinese Pharmacopeia*, their minimum total content in decoction pieces is 0.7% [1]. Modern pharmacological studies have shown that the coumarins of PF play a double role in pharmacological action and toxicity. XIA *et al.* found that the possible toxic substances were mainly rich in the ethyl acetate extract and the *n*-butanol extract, which are highly associated with the content of coumarins [62]. Moreover, other studies suggested that psoralen and isopsoralen had certain hepatotoxicity in zebrafish, mice and rats [63, 64]. The median lethal dose (LD_{50}) of psoralen and isopsoralen in mice was 638.69 and 351.72 $mg \cdot kg^{-1}$, respectively [65]. On the other hand, two benzofuran glycosides of PF had potential hepatotoxicity. Psoralenoside and isopsoralenoside were rich in aqueous extract of PF and quickly absorbed into the circulation system, before being metabolized into excessive psoralen and isopsoralen in the gastrointestinal microenvironment, leading to liver injury [66].

Flavonoids

Several flavonoids in PF exhibited stronger *in vitro* toxicity than coumarins, such as bavachin, bavachinin and isobavachalcone. Bavachin induced a significant increase in the production of reactive oxygen species (ROS), aggravating mitochondrial damage in HepG2 cells [67]. Bavachinin had strong cytotoxic effect on HepaRG cells, and the underlying mechanism was associated with oxidative damage *via* the p38/JNK MAPK pathways [57].

Monoterpene phenols

It was found that bakuchiol induced nephrotoxicity and hepatotoxicity [68]. Bakuchiol exhibited obvious toxicity to HK-2 cells, and its combination with psoralen aggravated cell damage [39]. With regard to hepatotoxicity, after treatment with bakuchiol at 52.5 $mg \cdot kg^{-1} \cdot d^{-1}$ for six weeks, the transaminase activities of rats were enahnced, and the expression of bile acid transporter-related proteins significantly changed [59]. Bakuchiol also inhibited the growth of HepG2 cells, with the half maximal inhibitory concentration (IC_{50}) of 41.3 $\mu mol \cdot L^{-1}$ [69].

Detoxification Methods

Detoxification by compatibility

Compatibility is one of the most classical principles in TCM theories, with synergistic effect and detoxification compatibility. There are many PF-related prescriptions compatible with other herbs that have been recorded in TCM books and widely used in clinical applications. Common compatible herbs with PF include Myristicae Semen (MS), Juglandis Semen (JS), Eucommiae Cortex (EC), and Cistanches Herba (CH), *etc.* We summarized the combination effects and possible mechanisms involved (Table 3). The underlying detoxification mechanisms and profound connotation of classical prescriptions require further studies, which will help to reveal the key point of safe use of herbal combination.

The metabolic process of main ingredients of PF changes, during combined use with other medicines, while the pharmacokinetics parameters of some compositions also change (Table 4). TANG *et al.* simultaneously determined the multiple compounds of Xianling Gubao Capsules in a reversed pharmacodynamic-pharmacokinetics study, and found that coumarins and prenylated flavonoids from PF had high exposure and profiled the pharmacokinetic features of representative substances [76]. ZHAO *et al.* investigated the compatibility from the perspective of pharmacokinetics and drug metabolism, and found that glycyrrhetinic acid, one of the main components of *Glycyrrhiza uralensis* Fisch., might increase renal toxicity by inhibiting the metabolism of PF by CYP450 enzyme [72]. In addition, some studies focused on formula decomposition and toxicity comparison, and some representative components of PF were selected to preliminarily screen out the crucial compatible herbs and identify its composition and to explore the detoxification mechanism. NING *et al.* utilized an effective and high-sensitive model of zebrafish to screen the detoxification compatible medicines with PF, and found that EC exhibited the stronest effects on attenuating the toxicity of PF. Further studies revealed that the aucubin of EC reduced the hepatoxicity induced by psoralen, which were associated with the HIF-1 pathway, chemical carcinogenic pathway and glutathione metabolic pathway [74].

Detoxification by processing

Processing is an equivalently important method to attenuate the toxicity of herbs, according to TCM theories. There are two traditional processing methods of PF, which were recorded in medical books and have been widely used nowadays, namely the alcohol soaking and water rinsing method and the salt processing method. The former origin-

Table 2 Characterization of the potential toxic compounds of PF

Constituents	Structural types	Organs	Experimental models	Mechanisms	Related targets	Reference
Psoralen	Coumarin	The liver	Rats	Inducing the bile acid transporters	CYP7A1, BSEP, MRP2, SULT2A1, FXR and MRP3	[46]
			Liver microsome of mice	Inducing th activity and expression of CYP450 enzymes	CYP3A11 and CYP2E1	[46]
			HuH-7 and HepaRG cells	Inducing the activity of CYP450 enzymes	CYP3A4	[47]
			HepG2 cells	Inducing hepatocyte apoptosis by the endoplasmic reticulum stress	Grp78, PERK, eIF2α, ATF4 and ATF6	[48]
		The kidneys	Male mice	Affecting renal organic ion transporters	OCT1, OCT2, OCTN1, OCTN2, OAT1, OAT3, URAT1, GLUT9 and MRP4	[46]
		The reproductive system	Female rats	Accelerating estrogen metabolism	UGT1A6 and CYP1A1	[49, 50]
		Embryonic development	Zebrafish	Inducing oxidative stress, apoptosis and lipid metabolism pathways	Keap1, Nrf2, Mn-sod, Cu/Zn-sod, p53, Puma, Bax, Bcl-2, Apaf-1, Caspase-9, Caspase-3, Hmgcra, Pparα and Fas	[47]
Isopsoralen	Coumarin	The liver	Rats	Inducing the bile acid transports	CYP7A1, BSEP, MRP2, MRP3, SULT2A1 and FXR; NTCP, MDR1, ABCG5, ABCG8, and OSTα	[46, 52]
			Liver microsome of mice	Inducing the activity and expression of CYP450 enzymes	CYP3A11 and CYP2E1	[46]
			Zebrafish	Reducing the antioxidant capacity of the liver	LFABP, GSTP2 and SODL	[51]
			HepG2 cells	Inducing the bile acid transports	MRP2 and MRP3	[53]
		The kidneys	Male mice	Affecting renal organic ion transporters	OCT1, OCT2, OCTN1, OCTN2, OAT1, OAT3, URAT1, GLUT9 and MRP4	[46]
Psoralidin	Coumarin	The liver	Female mice	Inducing idiosyncratic liver injury by activating the inflammasome	NLRP3, IL-1β, TNF-α, Caspase-1 and ROS	[54]
Bavachin	Flavonoid	The liver	Human UGT1A1 enzyme	Inhibiting bilirubin metabolism	UGT1A1	[55]
			HepG2 cells	Inducing the mitochondrial damage by endoplasmic reticulum stress	ROS, Mfn2, Akt, ATF4, CHOP and XBP1s	[56]
Bavachinin	Flavonoid	The liver	Human UGT1A1 enzyme	Inhibiting bilirubin metabolism	UGT1A1	[55]
			HepaRG cells	Inducing oxidative stress	P38, p-P38, JNK, p-JNK and ROS	[57]
Isobavachalcone	Flavonoid	The liver	Human UGT1A1 enzyme	Inhibiting bilirubin metabolism	UGT1A1	[55]
Bakuchiol	Monoterpene phenol	The kidneys	HK-2 cells	With obvious cytotoxicity		[39]
		The liver	Mice	Altering the bile acid transport receptor	NTCP	[58]
			Rats	Inducing lipid metabolism disorder	CYP7A1, HMG-CoA, BSEP, PPARα and SREBP-2	[59]

SHI Zhuo, *et al.* / *Chin J Nat Med*, 2022, **20**(11): 805-813

Table 3 The compatibility effects with PF and possible mechanisms

No.	PF-herbal medicine	Experimental model	Dose of FP (raw drug)	Duration	Combination effect	Mechanism	Reference
1	PF-Rehmanniae Radix	Rats	4.05 g·kg^{-1}	28 d	Reducing hepatotoxicity	Regulating body temperature and ATPase activity	[70]
2	PF-Epimedii Folium	Rats	0.22 g·kg^{-1}	1 d	Increasing hepatotoxicity	Inducing idiosyncratic hepatotoxicity under immunological stress conditions	[71]
3	PF-Paeoniae Radix Rubra	Rats	3.75 g·kg^{-1}	1 d	Reducing hepatotoxicity	Regulating arachidonic acidmetabolism and glycerophospholipid metabolism pathways	[36]
4	PF-Glycyrrhizae Radix et Rhizoma	Rats	40 g·kg^{-1}	1 d	Increasing renal toxicity	The absorbance of bakuchiol increased, and its clearance was prolonged.	[72]
5	PF-Eucommiae Cortex	Rats	0.68 g·kg^{-1}	6 w	Increasing bioactivity during treatmentMenopausal syndrome	Exerting the greatest estrogen-like effects	[73]
6	PF-Eucommiae Cortex	Zebrafish	200 μmol·L^{-1}	6 dpf	Reducing toxicity	The gene expression of immune activation and toxicity decreased.	[74]
7	PF-Cnidiic Fructus	Mice	3.6 g·kg^{-1}	6 w	The inhibitory effect on mammary cancer metastasis to bone was enhanced	Regulating OPG/RANKEL secretion ratio	[75]

Table 4 Pharmacokinetic parameters of compounds in PF

Oral medicines	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (mg·L^{-1})	AUC_{0-t} (mg·h·L^{-1})	CL (h·L^{-1}·kg^{-1})	Reference
PF extract						
Psoralen	2.67 ± 0.65	9.00 ± 1.67	3,970 ± 1.26	41,140 ± 16.20	0.02 ± 0.01	[79]
Isopsoralen	2.97 ± 0.87	10.00 ±1.27	2,130 ± 0.82	25,310 ± 9.40	0.02 ± 0.01	[79]
Psoralenoside	3.49 ± 0.45	2.58 ± 0.59	1,460 ± 0.24	12,010 ± 2.47	4.38 ± 1.02	[79]
Isopsoralenoside	5.64 ± 3.13	2.58 ± 0.59	2,580 ± 1.60	16,820 ± 6.45	2.56 ± 0.88	[79]
Psoralidin	25.15 ± 2.08	1.08 ± 0.88	1.09 ± 0.34	35.61 ± 1.31	191.33 ± 7.61	[80]
Bavachin	24.89 ± 4.73	1.00 ± 0.61	2.71 ± 0.83	100.59 ± 28.66	74.15 ± 23.08	[80]
Isobavachalcone	22.21 ± 6.15	2.00 ± 0.00	2.35 ± 0.44	75.96 ± 10.16	136.69 ± 35.11	[80]
Neobavaisoflavone	8.88 ± 5.15	24.00 ± 0.00	3.63 ± 1.23	88.46 ± 18.40	140.67 ± 21.90	[80]
Bakuchiol	10.22 ± 5.54	2.8 ± 1.10	395.73 ± 107.45	4,516 ± 516	7.18 ± 1.54	[81]
PF combinated with other herbal medicines						
Psoralen (compatibility with *Semen myristicae*)	9.22 ± 2.44	9.33 ± 2.73	7.91 ± 1.34	130.92 ± 18.72	139.03 ± 25.96	[82]
Psoralen (Sishen Wan)	4.28 ± 0.68	8.25 ± 0.71	7.85 ± 0.78	99.49 ± 16.58	200.42 ± 33.46	[83]
Isopsoralen (compatibility with *Semen myristicae*)	11.40 ± 6.60	9.33 ± 2.73	3.89 ± 0.54	69.49 ± 9.05	25.85 ± 58.57	[82]
Isopsoralen (Sishen Wan)	4.97 ± 1.25	8.25 ± 0.71	3.53 ± 0.62	49.23 ± 8.50	400.91 ± 82.75	[83]
Bakuchiol (compatibility with Glycyrrhizae Radix et Rhizoma)	8.65 ± 4.24	3.6 ± 0.89	575.16 ± 148.90	6,067.24 ± 416.01	5.50 ± 1.03	[81]

ated from *Lei's Treatise on Processing of Drugs* and is the oldest detoxification method of PF. Modern studies have found that the content of some ingredients decrease when they are soaked in alcohol, including psoralen, isopsoralen, psoralenoside and isopsoralenoside, while psoralenoside and isopsoralenoside are transformed into psoralen and isopsoralen when being steamed. About 50% of the toxic components can be reduced by this method, and more potential toxics of PF may be alcohol-soluble [77]. Recently, SONG *et al.* has used 3D cultured human liver organoids combined with

high connotation imaging to evaluate the detoxification of PF processed products, and verified that the hepatoxicity of PF decreased by the alcohol soaking and water rinsing method [78]. With regard to the salt processing method, XIA *et al.* found that it obviously alleviated liver injury induced by PF [62]. It is also listed in *Chinese Pharmacopoeia* due to the enhanced efficacy of PF.

Conclusions

PF has a long history of clinical application with good theraputic effect and has been widely used in many countries. However, little record about the toxicity of PF was found in ancient medical books, and PF is still excluded from the list of toxic herbs according to *Chinese Parmacopoeia* [1]. However, the prominent liver injury caused by PF has attracted much attention worldwide. It is urgent to clarify its toxic substances and hepatotoxic mechanism. Although some efforts have been devoted to the safety of PF, the onset events and toxic molecules remain unclear. Integrative multi-omics research, high-sensitive and high-throughput model, and computational chemistry methods will provide new insights into this topic. In this paper, we have presented a comprehensive summary of the botany, potential risks, toxic characteristics, underlying mechanisms and detoxification methods of PF. Systematic research of the relationship between the pharmacological effects and its toxicity will not only improve its safe use but also facilitate its drug development.

References

[1] Pharmacopoeia of the People's Republic of China (2020). Vol 1 [S]. 2020: 195.

[2] Li A, Gao MH, Zhao N, *et al*. Acute liver failure associated with Fructus Psoraleae: a case report and literature review [J]. *BMC Complement Altern M*, 2019, **19**: 84-88.

[3] Nam SW, Baek JT, Lee DS, *et al*. A case of acute cholestatic hepatitis associated with the seeds of *Psoralea corylifolia* (Boh-Gol-Zhee) [J]. *Clin Toxicol*, 2005, **43**: 589-591.

[4] Wang Y, Hong C, Zhou C, *et al*. Screening antitumor compounds psoralen and isopsoralen from *Psoralea corylifolia* L. Seeds [J]. *Evid Based Complement Alternat Med*, 2011, **2011**: 363052.

[5] Wu C, Sun Z, Ye Y, *et al*. Psoralen inhibits bone metastasis of breast cancer in mice [J]. *Fitoterapia*, 2013, **91**: 205-210.

[6] Lu H, Zhang L, Liu D, *et al*. Isolation and purification of psoralen and isopsoralen and their efficacy and safety in the treatment of osteosarcoma in nude rats [J]. *Afr Health Sci*, 2014, **14**: 641-647.

[7] Szliszka E, Czuba ZP, Sedek L, *et al*. Enhanced TRAIL-mediated apoptosis in prostate cancer cells by the bioactive compounds neobavaisoflavone and psoralidin isolated from *Psoralea corylifolia* [J]. *Pharmacol Rep*, 2011, **63**: 139-148.

[8] Yang Z, Huang JH, Liu SF, *et al*. The osteoprotective effect of psoralen in ovariectomy-induced osteoporotic rats *via* stimulating the osteoblastic differentiation from bone mesenchymal stem cells [J]. *Menopause*, 2012, **19**: 1156-1164.

[9] Wang D, Li F, Jiang Z. Osteoblastic proliferation stimulating activity of *Psoralea corylifolia* extracts and two of its flavonoids [J]. *Planta Med*, 2001, **67**: 748-749.

[10] Xiong Z, Wang D, Xu Y, *et al*. Osteoblastic differentiation bioassay and its application to investigating the activity of fractions and compounds from *Psoralea corylifolia* L. [J]. *Pharmazie*, 2003, **58**: 925-928.

[11] Xiao G, Li G, Chen L, *et al*. Isolation of antioxidants from *Psoralea corylifolia* fruits using high-speed counter-current chromatography guided by thin layer chromatography-antioxidant autographic assay [J]. *J Chromatogr A*, 2010, **1217**: 5470-5476.

[12] Lee MH, Kim JY, Ryu JH. Prenylflavones from *Psoralea corylifolia* inhibit nitric oxide synthase expression through the inhibition of I-κB-α degradation in activated microglial cells [J]. *Biol Pharm Bull*, 2005, **28**: 2253-2257.

[13] Anand KK, Sharma ML, Singh B. Anti-inflamatory, antipyretic& analgesic properties of bavachinin-a flavanone isolated from seeds of *Psoralea corylifolia* Linn. (Babchi) [J]. *Indian J Exp Biol*, 1978, **16**: 1216-1217.

[14] Matsuda H, Kiyohara S, Sugimoto S. Bioactive constituents from Chinese natural medicines. XXXIII. Inhibitors from the seeds of *Psoralea corylifolia* on production of nitric oxide in lipopolysaccharide-activated macrophages [J]. *Biol Pharm Bull*, 2009, **32**: 147-149.

[15] Lee SW, Yun BR, Kim MH, *et al*. Phenolic compounds isolated from *Psoralea corylifolia* inhibit IL-6-induced STAT3 activation [J]. *Planta Med*, 2012, **78**: 903-906.

[16] Khatune NA, Islam ME, Haque ME, *et al*. Antibacterial compounds from the seeds of *Psoralea corylifolia* [J]. *Fitoterapia*, 2004, **75**: 228-230.

[17] Katsura H, Tsukiyama RI, Suzuki A, *et al*. *In vitro* antimicrobial activities of bakuchiol against oral microorganisms [J]. *Antimicrob Agents Chemother*, 2001, **45**: 3009-3013.

[18] Xin D, Wang H, Yang J, *et al*. Phytoestrogens from *Psoralea corylifolia* reveal estrogen receptor-subtype selectivity [J]. *Phytomedicine*, 2010, **17**: 126-131.

[19] Liu X, Nam JW, Song YS, *et al*. Psoralidin: a coumestan analogue, as a novel potent estrogen receptor signaling molecule isolated from *Psoralea corylifolia* [J]. *Bioorg Med Chem Lett*, 2014, **24**: 1403-1406.

[20] Kong LD, Tan RX, Woo AY, *et al*. Inhibition of rat brain monoamine oxidase activities by psoralen and isopsoralen: implications for the treatment of affective disorders [J]. *Pharmacol Toxicol*, 2001, **88**: 75-80.

[21] Yi LT, Li YC, PanY, *et al*. Antidepressant-like effects of psoralidin isolated from the seeds of *Psoralea corylifolia* in the forced swimming test in mice [J]. *Prog Neuropsychopharmacol Biol Psychiatry*, 2008, **32**: 510-519.

[22] Seo E, Oh YS, Kim D, *et al*. Protective role of *Psoralea corylifolia* L. seed extract against hepatic mitochondrial dysfunction induced by oxidative stress or aging [J]. *Evid Based Complement Alternat Med*, 2013, **2013**: 678028.

[23] Im AR, Chae SW, Zhang GJ, *et al*. Neuroprotective effects of *Psoralea corylifolia* Linn. seed extracts on mitochondrial dysfunction induced by 3-nitropropionic acid [J]. *BMC Complem Altern M*, 2014, **14**: 370.

[24] Li X, Lee YJ, Kim YC, *et al*. Bakuchicin induces vascular relaxation *via* endothelium-dependent NO-cGMP signaling [J]. *Phytother Res*, 2011, **25**: 1574-1578.

[25] Tian WS, Lan S, Zhang L, *et al*. Safety evaluation and risk control measures of *Psoralea corylifolia* [J]. *Chin J Chin Mater Med*, 2017, **42**: 4059-4066.

[26] Zhu Y, Li YG, Wang Y, *et al*. Analysis of clinical characteristics in 595 patients with herb-induced liver injury [J]. *Chin J Integr Med*, 2016, **36**: 44-48.

[27] Wang L, Wang Y, Wee A, *et al*. Clinicopathological features of Bu Gu Zhi-induced liver injury, a long-term follow-up cohort study [J]. *Liver Int*, 2020, **40**: 571-580.

[28] Cheung WI, Tse ML, Ngan T, *et al*. Liver injury associated

with the use of Fructus psoraleae (Bol-Gol-Zhee or Bu-Gu-Zhi) and its related proprietary medicine [J]. *Clin Toxicol*, 2009, **47**: 683.

[29] Liu YL, Ge FL, Zhu JX, *et al*. Re-evaluation of liver injury associated with Buguzhi Preparations based on passive monitoring data and hospital cases [J]. *Chin J Chin Mater Med*, 2019, **44**: 4272-4276.

[30] Zhou K, Dai Z, Liu ZB, *et al*. Aqueous extract of *Psoralea corylifolia* induced liver injury in rats [J]. *Tianjin J Tradit Chin Med* , 2013, **32**: 221-224.

[31] Zhao X, Cai TT, Guo X, *et al*. Chronic toxicity of salt *Psoralea corylifolia* L. aqueous extract in male and female rats [J]. *Chin J Pharmacovigilance*, 2021, **18**: 6.

[32] Wang J, Jiang Z, Ji J, *et al*. Evaluation of hepatotoxicity and cholestasis in rats treated with EtOH extract of Fructus psoraleae [J]. *J Ethnopharmacol*, 2012, **144**(1): 73-81.

[33] Duan J, Dong W, Xie L, *et al*. Integrative proteomics-metabolomics strategy reveals the mechanism of hepatotoxicity induced by Fructus Psoraleae [J]. *J Proteomics*, 2020, **221**: 103767.

[34] Tang JF, Wang XY, Wen Q, *et al*. Idiosyncratic hepatotoxicity evaluation of Zhuangguguanjie Wan mediated by immune stress [J]. *Acta Pharm Sin*, 2017, **52**: 1033-1040.

[35] Wang XY, Li WX, Zhang H, *et al*. The mechanism of Fructus Psoralea induced idiosyncratic liver injury based on metabolomics [J]. *Chin J Pharmacovigilance*, 2021, **18**: 1014-1019.

[36] Wu WX, Guo S, Wu LP, *et al*. Paeoniae Rubra Radix decreases the hepatotoxicity of Psoraleae Fructus in an immunologically stressed rat model: a metabolic network analysis [J]. *Acta Pharm Sin*, 2021, **56**: 7.

[37] Hou XD, Song LL, Cao YF, *et al*. Pancreatic lipase inhibitory constituents from Fructus Psoraleae [J]. *Chin J Nat Med*, 2020, **18**(5): 369-378.

[38] Wang X, Lou YJ, Wang MX, *et al*. Furocoumarins affect hepatic cytochrome P450 and renal organic ion transporters in mice [J]. *Toxicol Lett*, 2012, **209**: 67-77.

[39] Jiang F, Zhou XR, Wang Q, *et al*. Cytotoxic effect and mechanism of bakuchiol and bakuchiol combined with psoralen on HK-2 cell [J]. *Chin J Pharmacol Toxicol*, 2010, **2020**(1): 50-58.

[40] Wang Y, Zhang H, Jiang JM, *et al*. Multiorgan toxicity induced by EtOH extract of Fructus Psoraleae in Wistar rats [J]. *Phytomedicine*, 2019, **58**: 152874-152884.

[41] Diawara MM, Chavez KJ, Hoyer PB, *et al*. A novel group of ovarian toxicants: the psoralens [J]. *J Biochem Mol Toxicol*, 1999, **13**: 195-203.

[42] Neumann, Norbert J. Rapid decrease of phototoxicity after puva bath therapy with 8-methoxypsoralen [J]. *Arch Dermatol*, 1996, **132**: 1394.

[43] Resneck J, Kimball AB. Orally administered extract decreases psoralen-UVA-induced phototoxicity, pigmentation, and damage of human skin [J]. *J Am Acad Dermatol*, 2004, **50**: 41-9.

[44] Wei MM, Wang SY, Yang W, *et al*. Chemical constituents of Psoraleae Fructus and its main toxic ingredients [J]. *Chin J Exper Tradit Med Form*, 2019, **25**(7): 13.

[45] Zhou QH, Zhu YD, Zhang F, *et al*. Interactions of drug-metabolizing enzymes with the Chinese herb Psoraleae Fructus [J]. *Chin J Nat Med*, 2019, **17**(11): 13.

[46] Wang Y, Zhang H, Jiang JM, *et al*. Hepatotoxicity induced by psoralen and isopsoralen from Fructus Psoraleae: Wistar rats are more vulnerable than ICR mice [J]. *Food Chem Toxicol*, 2019, **125**: 133-140.

[47] Liu YT, Flynn TJ. CYP3A4 inhibition by *Psoralea corylifolia* and its major components in human recombinant enzyme, differentiated human hepatoma HuH-7 and HepaRG cells [J]. *Toxicol Rep*, 2015, **2**: 530-534.

[48] Yu YL, Yu RL, Men WJ, *et al*. Psoralen induces hepatic toxicity through PERK and ATF6 related ER stress pathways in HepG2 cells [J]. *Toxicol Mech Methods*, 2020, **30**: 39-47.

[49] Diawara MM, Kulkosky PJ. Reproductive toxicity of the psoralens [J]. *Pediatr Pathol Mol Med*, 2003, **22**: 247-258.

[50] Xu M, Tian XY, Leung KSY, *et al*. Embryotoxicity of *Psoralea corylifolia* L. : *in vivo* and *in vitro* studies [J]. *Birth Defects Res B Dev Reprod Toxicol*, 2012, **95**: 386-394.

[51] Zhang Y, Zhang Y, Li J, *et al*. The role of hepatic antioxidant capacity and hepatobiliary transporter in liver injury induced by isopsoralen in zebrafish larvae [J]. *Hum Exp Toxicol*, 2019, **38**: 36-44.

[52] Huang JY, Wang Q, Bi YN, *et al*. Effect of isopsoralen on hepatic function and bile acid transporters in SD rats with different administration periods [J]. *Chin Pharmacol Bull*, 2019, **35**: 260-264.

[53] Zhou K, Wang AH, Chai LJ. Effects of bakuchiol on HepG2 cytotoxicity and BSEP, NTCP, FXR, CYP7A1 [J]. *J Toxicol*, 2015, **29**: 193-196.

[54] Wang Y, Xu G, Wang Z, *et al*. Psoralidin, a major component of Psoraleae Fructus, induces inflammasome activation and idiosyncratic liver injury [J]. *Int Immunopharmacol*, 2021, **92**: 107352.

[55] Wang XX, Lv X, Li SL, *et al*. Identification and characterization of naturally occurring inhibitors against UDP-glucuronosyltransferase 1A1 in Fructus Psoraleae (Bu-gu-zhi) [J]. *Toxicol Appl Pharmacol*, 2015, **289**: 70-78.

[56] Yang Y, Tang XL, Hao FR, *et al*. Bavachin induces apoptosis through mitochondrial regulated ER stress pathway in HepG2 cells [J]. *Biol Pharm Bull*, 2018, **41**: 198-207.

[57] Wang S, Wang M, Wang M, *et al*. Bavachinin induces oxidative damage in HepaRG cells through p38/JNK MAPK pathways [J]. *Toxins (Basel)*, 2018, **10**: 154-165.

[58] Bi YN, Li Z, Zhou K, *et al*. Influence of Bakuchiol on liver function and bile acid transporters BSEP and NTCP in mouse [J]. *Tianjin J Tradit Chin Med*, 2015, **34**: 222-225.

[59] Li ZJ, Abulizi A, Zhao GL, *et al*. Bakuchiol contributes to the hepatotoxicity of *Psoralea corylifolia* in rats [J]. *Phytother Res*, 2017, **31**: 1265-1272.

[60] Jois HS, Manjunath BL, Venkatarao S. Chemical examination of the seeds of *Psoralea corylifolia* [J]. *J Indian Chem Soc*, 1933, **10**: 41.

[61] Jois HS, Manjunath BL. Identity of isopsoralen, a constituent of the seeds of *Psoralea corylifolia* L. with angelicin from the roots of *Angelica archangelica* L [J]. *Ber Deut Chem Ges*, 1936, **69**: 964.

[62] Xia YN, Yu LY, Wang DJ, *et al*. Study on the effect of deficiency of Kidney Yang, Spleen deficiency of animal model before and after different doses of Psoralea stir-baked with salt solution [J]. *Asia-Pacific Tradit Med*, 2016, **12**: 5-9.

[63] Chen Y, Wang M, Song J, *et al*. Effect of extract ethanol and water decoction of *Psoralea corylifolia* L. on bone development and their toxicities in zebrafish [J]. *Chin J Pharmacol Toxicol*, 2017, **31**: 661-669.

[64] Vassallo JD, Hicks SM, Daston GP, *et al*. Metabolic detoxification determines species differences in coumarin-induced hepatotoxicity [J]. *Toxicol Sci*, 2004, **80**: 249-257.

[65] Bai RY, Zhang PY, Bi YN, *et al*. Acute toxicity and drug interaction of psoralen and isopsoralen [J]. *Drug Eval Res*, 2018, **41**: 1068-1072.

[66] Yan DM, Gao XM, Kang LY, *et al*. Transitional features of benzofuran glycosides part from Psoraleae Fructus in rat plasma [J]. *Chin J ExpTradit Med Form*, 2015, **21**: 85-88.

[67] Li ZJ, Abudumijiti A, Xu DQ, *et al*. Quantitative proteomics

analysis of Fructus Psoraleae-induced hepatotoxicity in rats [J]. *Chin J Nat Med*, 2020, **18**(2): 123-137.
[68] Yao Z, Li S, Qin Z, *et al*. Characterization of human UDP-glucuronosyltransferases responsible for glucuronidation and inhibition of norbakuchinic acid, a primary metabolite of hepatotoxicity and nephrotoxicity component bakuchiol in *Psoralea corylifolial* [J]. *RSC Advances*, 2017, **83**: 7.
[69] Zhou K, Bi YN, Shi H. Psoralen induced bile acid accumulation and cytotoxicity by inhibiting MRP2 and MRP3 in HepG2 cells [J]. *Chin Pharmacol Bull*, 2015, **31**: 1112.
[70] Song XL, Li F, Cui GZ. Effect of Psoraleae Fructus and Rehmanniae Radix on body temperature and ATPase activity in rats [J]. *Chin J Exp Tradit Med Form*, 2013, **19**: 160-162.
[71] Gao Y, Wang ZL, Tang JF, *et al*. New incompatible pair of TCM: Epimedii Folium combined with Psoraleae Fructus induces idiosyncratic hepatotoxicity under immunological stress conditions [J]. *Front Med*, 2020, **14**: 68-80.
[72] Zhao ZJ, Gong Z, Shi SZ, *et al*. Toxicokinetics of bakuchiol, hepatic and renal toxicity in rats after single oral administration of Psoraleae Fructus and combination with Glycyrrhizae Radix et Rhizoma [J]. *Chin J Chin Mater Med*, 2015, **40**: 6.
[73] Xiong JL, Cai XY, Zhang ZJ, *et al*. Elucidating the estrogen-like effects and biocompatibility of the herbal components in the Qing' E formula [J]. *J Ethnopharmacol*, 2021, **283**: 114735.
[74] Ning Q, Liu ZQ, Wei YJ, *et al*. Analysis on the compatibility of Psoralen based on the toxicity evaluation of zebrafish [J]. *J Nanjing Uni Tradit Chin Med*, 2021, **37**: 8.
[75] Cheng XF, Liu S, Jin H, *et al*. Study on characteristics of absorption into blood of common Cnidium Fruit-Malaytea Scurfpea Fruit in breast cancer bone metastasis nude mice model [J]. *Chin J Exp Tradit Med Form*, 2012, **18**: 176.
[76] Tang XY, Dai ZQ, Wu QC, *et al*. Simultaneous determination of multiple components in rat plasma and pharmacokinetic studies at a pharmacodynamic dose of Xian-Ling-Gu-Bao Capsule by UPLC-MS/MS [J]. *J Pharm Biomed Anal*, 2019, **177**: 112836.
[77] Wang XY, Li WX, Zhang H, *et al*. The toxicity of Psoraleae Fructus and its main components in L02 cells [J]. *Tradit Chin Med Res*, 2020, **33**: 59-63.
[78] Song D, Cheng SS, Li PY, *et al*. Attenuating the potential hepatotoxicity of Psoraleae Fructus by pre-processing: the alcohol soaking and water rinsing method [J]. *Acta Pharm Sin*, 2020, **55**: 7.
[79] Wang YF, Liu YN, Xiong W, *et al*. A UPLC-MS/MS method for *in vivo* and *in vitro* pharmacokinetic studies of psoralenoside, isopsoralenoside, psoralen and isopsoralen from *Psoralea corylifolia* extract [J]. *J Ethnopharmacol*, 2014, **151**: 609-617.
[80] Yang YF, Zhang YB, Chen ZJ, *et al*. Plasma pharmacokinetics and cerebral nuclei distribution of major constituents of psoraleae fructus in rats after oral administration [J]. *Phytomedicine*, 2018, **38**: 166-174.
[81] Huo TG, Fang Y, Zhang YH, *et al*. Liver metabonomics study on the protective effect of glycyrrhetinic acid against realgar-induced liver injury [J]. *Chin J Nat Med*, 2020, **18**(2): 138-147.
[82] Tang CJ, Shi B, Xiu YF, *et al*. Pharmacokinetic study on psoralen and isopsoralen in "Ershen Decoction" [J]. *J Shanghai Univ Tradit Chin Med*, 2011, **7**: 72-74.
[83] Tang CJ, Shi B, Xiu YF, *et al*. Pharmacokinetics of psoralen and isopsoralen in Sishenwan Decoction in rats [J]. *Chin Tradit Pat Med*, 2012, **2**: 248-251.

Cite this article as: SHI Zhuo, GAO Jing, PAN Jinchao, ZHANG Zuqi, ZHANG Guangchen, WANG Yuguang, GAO Yue. A Systematic Review of Psoraleae Fructus [J]. *Chin J Nat Med*, 2022, **20**(11): 805-813.