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Interactions of drug-metabolizing enzymes with the Chinese herb Psoraleae Fructus

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[ABSTRACT] Psoraleae Fructus (the dried fruits of *Psoralea corylifolia*), one of the most frequently used Chinese herbs in Asian countries, has a variety of biological activities. In clinical settings, Psoraleae Fructus or Psoraleae Fructus-related herbal medicines frequently have been used in combination with a number of therapeutic drugs for the treatment of various human diseases, such as leukoderma, rheumatism and dysentery. The use of Psoraleae Fructus in combination with drugs has aroused concern of the potential risks of herb-drug interactions (HDI) or herb-endobiotic interactions (HEI). This article reviews the interactions between human drug-metabolizing enzymes and the constituents of Psoraleae Fructus; the major constituents in Psoraleae Fructus, along with their chemical structures and metabolic pathways are summarized, and the inhibitory and inductive effects of the constituents in Psoraleae Fructus on human drug-metabolizing enzymes (DMEs), including target enzyme(s), its modulatory potency, and mechanisms of action are presented. Collectively, this review summarizes current knowledge of the interactions between the Chinese herb Psoraleae Fructus and therapeutic drugs in an effort to facilitate its rational use in clinical settings, and especially to avoid the potential risks of HDI or HEI through human DMEs.

[KEY WORDS] Psoraleae Fructus; Cytochrome P450 enzymes (CYPs); Uridine diphosphate-glucuronosyltransferases (UGTs); Herb-drug interactions (HDI); Herb-endobiotic interactions (HEI).

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Introduction

Psoraleae Fructus (the dried fruits of *Psoralea corylifolia* L.), one of the most widely used Chinese herbs in Asian countries, has been widely used for the treatment of leucoderma and other skin diseases, cardiovascular diseases, nephritis, bone fracture and osteoporosis, as well as for the adjunctive treatment of several types of cancer [1]. In China and other Asian countries, Psoraleae Fructus is the most frequently used material for preparing herbal medicines, such as Fufang Psoraleae Fructus Keli and Psoraleae Fructus Injection, Algushadi yoga, Maheshwara ghrita, Ayorajodi lepa, and Bawchi tel [2]. Over the past two decades the biological activities of extracts or the bioactive compounds from *P. corylifolia* have been extensively studied [2-3]. In clinical settings, Psoraleae Fructus or Psoraleae Fructus-related herbal medicines have been frequently used in combination with a panel of therapeutic drugs for the treatment of various human diseases. The combination use of Psoraleae Fructus with therapeutic drugs has aroused great concerns on the potential risks of herb-drug interactions (HDI) or herb-endobiotic interactions (HEI), by both patients and clinical pharmacologists. In

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fact, several case reports have revealed that Psoraleae Fructus can lead to hyperbilirubinemia, liver injury and other side effects [4-5]. Therefore, it is essential to systematically investigate the interactions between the major constituents of Psoraleae Fructus, as well as the key proteins in the human body, especially for those enzymes that participate in the detoxification of drugs and toxic endogenous compounds. Over the past decade the major constituents in Psoraleae Fructus and their metabolic pathways in human tissues, along with the inhibitory and inductive effects of its constituents on human drug metabolizing enzymes (DMEs) have been well investigated. On the basis of these investigations, this review provides an extensive overview of the recent progress on the metabolic interactions between the Chinese herb Psoraleae Fructus and human DMEs. The major constituents in Psoraleae Fructus, along with their metabolic pathways and pharmacokinetic parameters are well-summarized. Meanwhile, the inhibitory and inductive effects of these constituents on human DMEs, including human cytochrome P450 enzymes (CYPs), UDP-glucuronosyltransferases (UGTs), and esterases, are also summarized. The information presented in this review will be extremely helpful for the rational use of the Chinese herb Psoraleae Fructus in clinical settings, and especially to avoid potential risks of HDI or HEI as a result of the inhibition or changes in the expression of human DMEs.

Major constituents of the Chinese herb Psoraleae Fructus

More than 90 kinds of compounds have been isolated from *P. corylifolia* [6-7], including coumarins, meroterpenes, flavonoids, chalcones, stigmasteroids, lipids, resins, and volatile oils, *etc*. Among these constituents, coumarins (psoralen, isopsoralidin, and psoralidin), flavonoids (bavachin, daidzin), chalcones (isobavachalcone) and several monoterpenoids (such as bakuchiol) have been validated as major constituents in the seeds of *P. corylifolia* (Fig. 1) [2]. Zhang *et al*. have quantitatively determined the contents of major constituents in the seeds of *P. corylifolia* and report that bakuchiol (5.24%), psoralenoside (1.57%), isopsoralenoside (1.45%), psoralen (0.52%), isopsoralen (0.39%), bavachinin (0.76%), corylin (0.06%), corylifol A (0.24%), psoralidin (0.24%), isobavachalcone (0.58%) and bavachalcone (0.05%) are abundant constituents in the seeds of *P. corylifolia* (Fig. 2) [8]. Over the past two decades, modern pharmacological investigations have demonstrated that both the crude extract of the seeds of *P. corylifolia* and its major constituents exhibited a wide range of biological activities, including estrogenic, antitumor, anti-oxidant, antimicrobial, antidepressant, anti-inflammatory, osteoblastic effects, as well as effects on enzyme activities [6]. It has been reported that the flavonoids and chalcones isolated from the seeds of *P. corylifolia* have been found with a wide variety of beneficial effects, including anti-inflammatory [9], antibacterial [10], anti-oxidative [11], anticancer [12], protein kinase inhibition activity [13-16], *etc*. The coumarins (such as psoralenoside) isolated from this herb have also been found to have a variety of biological activities, including antibacterial [17], osteoblastic [18], anti-tumor [19] and anti-oxidative [20], antimicrobial [21] and hepatoprotective [22] activity, *etc*. The first reported monoterpenoid compound isolated from the seeds of *P. corylifolia* is bakuchiol [23]; this compound has multiple activities, such as antimicrobial [24], osteoblastic [25], anti-tumor [26] and hepatoprotective [27] activity, *etc*. Recently, several oxygenated derivatives of bakuchiol were isolated from this herb and their antimicrobial activity was investigated [28].

Metabolism of major constituents in Psoraleae Fructus

In vitro metabolism of major constituents in Psoraleae Fructus

Over the past ten years the metabolic pathways for the major constituents in Psoraleae Fructus have been extensively studied in liver microsomes from both human and experimental animals. It has been found that most of the constituents in this herb can be metabolized by both phase I and phase II metabolizing enzymes in mammals. Qin *et al*. found that corylin can be readily metabolized by mammalian CYPs to generate a series of oxidative and hydrated metabolites, while this natural compound can also be metabolized by conjugative enzymes to form the corresponding O-glucuronide *O*-sulfate [29]. The metabolic pathways of corylin in human liver preparations are summarized in Fig. 3. Qin *et al*. also revealed that CYP1A, CYP1B1 and CYP2C19 are major contributors to the oxidative metabolism of corylin, while UGT1A1 is the key enzyme responsible for corylin-*O*-glucuronidation in the human liver [29]. Xu *et al*. investigated the phase I and phase II metabolic pathways of neobavaisoflavone *in vitro*, and the results clearly demonstrated that neobavaisoflavone can be rapidly metabolized into three oxidative metabolites and two *O*-glucuronides by human CYPs and UGTs, and the drug-metabolizing enzymes involved in these processes have been determined (Fig. 3) [30]. Bakuchiol can be metabolized by mammalian CYPs to generate a panel of oxidative metabolites; CYP1A2, CYP2B6, CYP2C19 and CYP3A4 are involved in the oxidative metabolism of this major constituent in Psoraleae Fructus [31-33]. Bakuchiol can be metabolized by CYP1A2, CYP2B6, CYP2C19, and CYP3A4 to form a set of oxidative metabolites. Meanwhile, UGT1A1, UGT1A3 and UGT2B15 have the ability to metabolize bakuchiol to form a mono-*O*-glucuronide [34]. Lv *et al*. reported that bavachinin can be *O*-glucuronidated by UGTs in human liver preparations, and UGT1A1, UGT1A3 and UGT1A8 are major contributors [35]. As shown in Fig. 3, psoralidin can be metabolized by both mammalian CYPs and UGTs. Psoralidin can be initially metabolized by CYP2C19 to form a hydroxylated metabolite [36], and this compound can also be metabolized by UGT1A1, UGT1A7, UGT1A8 and UGT1A9 to form two *O*-glucuronides [37]. The glucuronidation sites of psoralidin have been determined *via* NMR analysis of two biosynthesized

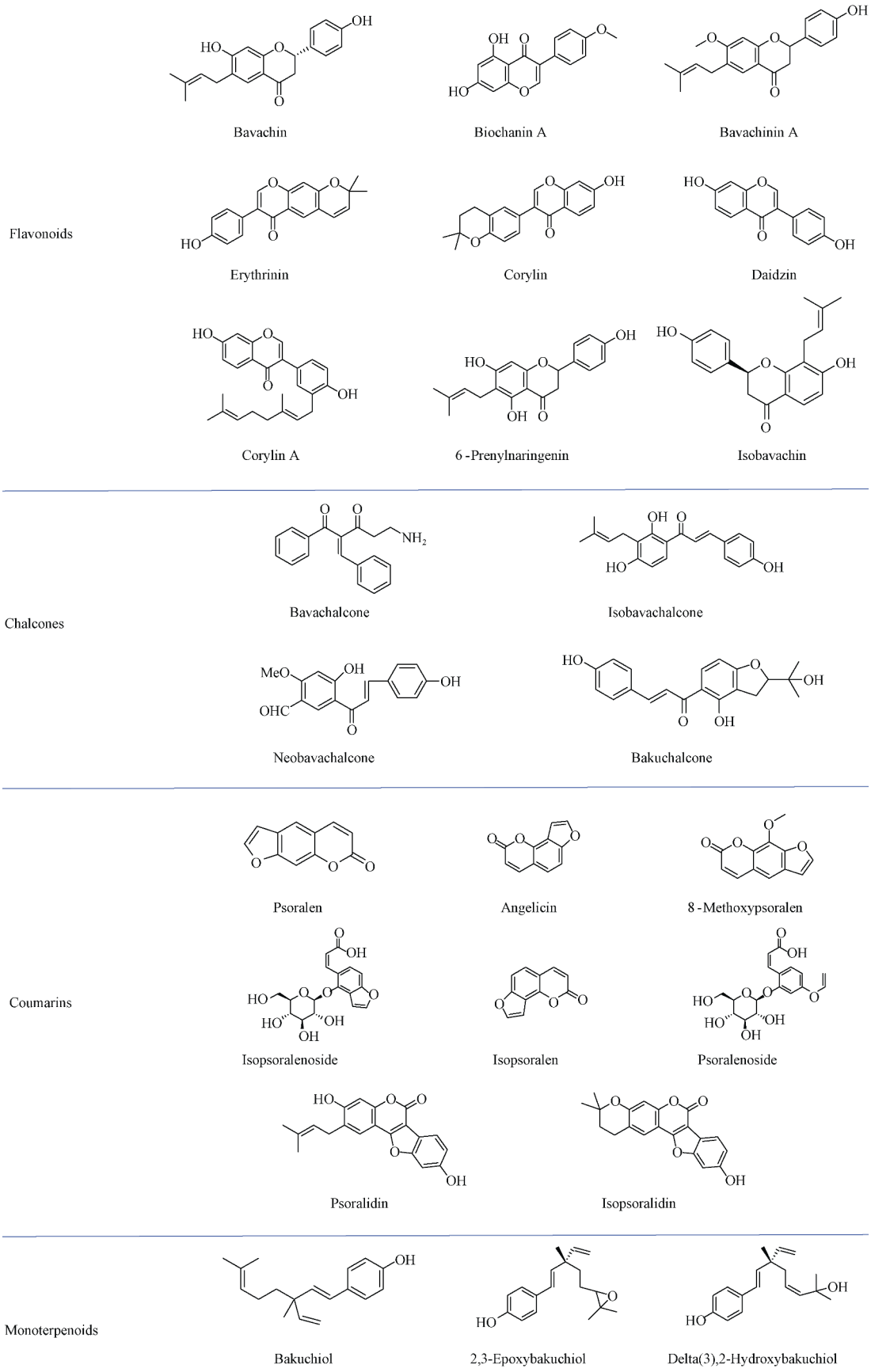


Fig. 1 Chemical structures of major active constituents in Psoraleae Fructus

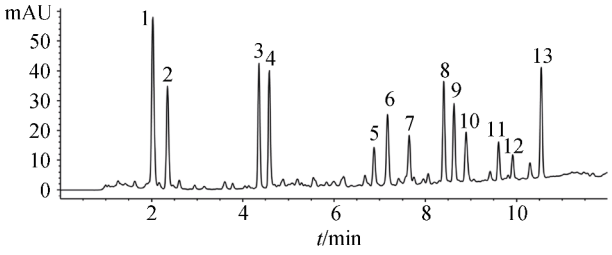


Fig. 2 Representative LC-UV chromatograms of the seeds of *P. corylifolia*. (1) psoralenoside, (2) isopsoralenoside, (3) psoralen, (4) isopsoralen, (5) bavachin, (6) neobavaisoflavone, (7) corylin, (8) isobavachalcone, (9) bavachinin, (10) psoralidin, (11) corylifol A, (12) bavachalcone, (13) bakuchiol [8]

O-glucuronides. Yang *et al*. investigated the differences in the metabolite profiles of psoralen/isopsoralen in liver microsomes from both humans and from six mammals [38]. Xie *et al*. analyzed the metabolites of bavachin in rat liver microsomes by LC-ESI-MS^n and identified some compounds *via* comparison to standards obtained by chemical synthesis [39], but the *in vitro* metabolic parameters of bavachin metabolism have not been reported.

In vivo metabolism of major constituents in Psoraleae Fructus

Besides the *in vitro* studies on the metabolism of major constituents in the Chinese herb Psoraleae Fructus, some groups have investigated the metabolism and pharmacokinetic behaviors of several major constituents Psoraleae Fructus *in vivo*. In 2015, Yao *et al*. investigated the metabolic fates in rats of six representative constituents in the seeds of *P. corylifolia* by ultra-performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry (UPLC/Q-TOF-MS) [40]. The results demonstrated that all tested compounds (including psoralen, psoralidin, bavachin, neobavaisoflavone, isobavachalcone and bakuchiol) could be rapidly absorbed into the circulation, while a total of 142 Psoraleae Fructus-related xenobiotics were identified or tentatively characterized in rat biofluids following oral administration of these single compounds or a crude extract of Psoraleae Fructus [40]. Ten metabolites, including oxidative and conjugative metabolites, have been detected in rat plasma, urine and fecal samples following oral administration of psoralen [40] (Data not shown). Similarly, a total of 12 metabolites (including hydroxylated and epoxidated metabolites, as well as the sulfate and glucuronide) were identified in rat plasma, urine and fecal samples, after oral administration of psoralidin [40]. Recently, Xue *et al*. investigated the metabolism of isobavachalcone in rats *in vivo*, and five phase I metabolites and ten phase II metabolites of this prenylated chalcone were identified in rat bile using LC-ESI-MS^n and LC-NMR after oral administration of isobavachalcone with a dosage of 50 mg·kg^{-1}[41]. Hu *et al*. investigated the metabolic fate of bakuchiol in rats by ultra-performance liquid chromatography/electrospray ionization–photo diode array–quadrupole time of flight–mass spectrometry (UPLC/ESI-PDA-QTOF-MS), a total of 11 metabolites were identified after oral administration of bakuchiol, including 6 in plasma, 10 in bile, 8 in urine and 2 in feces, and the major metabolic pathways of bakuchiol in rats were oxidation, hydroxylation, methylation, *O*-glucuronidation and *O*-sulfation [42]. Wang *et al*. isolated 12 metabolites from the urine and feces of rats after oral administration of bakuchiol and their chemical structures were fully elucidated by NMR [43]. Qian *et al*. studied the metabolism and pharmacokinetic behavior of bavachinin in rats following oral administration and found that bavachinin exhibited rapid oral absorption (T_{max} = 0.68 ± 0.21 h), high elimination ($T_{1/2}$ = 2.27 ± 1.63 h) and poor absolute bioavailability (5.27%) [44]. Wang *et al*. have developed a rapid and sensitive method for simultaneous determination of four major constituents from Psoraleae Fructus (including psoralenoside, isopsoralenoside, psoralen and isopsoralen) in biological samples and determined the pharmacokinetic parameters of these four constituents in rats following oral administration of the extract of Psoraleae Fructus at a dosage of 3870 mg·kg^{-1} (Table 3) [45]. These results demonstrate that psoralenoside and isopsoralenoside can be converted readily to psoralen and isopsoralen by intestinal microflora *via* deglucosylation.

Inhibition of human DMEs by Psoraleae Fructus and its major constituents

In view of the wide use of Psoraleae Fructus-related herbal medicines in clinical settings, the risks of herb-drug interactions (HDI) or herb-endobiotic interactions (HEI) *via* modulation of drug-metabolizing enzymes or drug transporters should be recognized in Psoraleae Fructus-associated therapy [46]. Over the past decade the modulatory effects of Psoraleae Fructus extract and its major constituents on key drug-metabolizing enzymes in the human liver, such as cytochrome P450 enzymes (CYPs), UDP-glucuronosyltransferases (UGTs) and carboxylesterases (CES), have been well-investigated, given that these enzymes play a pivotal role in the metabolic clearance of a wide variety of clinically used drugs [47-49].

CYP inhibition by Psoraleae Fructus and its constituents

Liu *et al*. investigated the inhibitory effects of four coumarins isolated from Psoraleae Fructus (including psoralen, isopsoralen, imperatorin and isoimperatorin) on seven human hepatic CYPs using human liver microsomes as the enzyme source. The results suggested that imperatorin and isoimperatorin showed strong inhibition of CYP1A2 and CYP2E1 [50]. In another study, Zhong *et al*. evaluated the inhibitory effects of psoralen and isopsoralen on five human hepatic CYPs and found that psoralen and isopsoralen displayed strong inhibitory effects on CYP1A2-mediated phenacetin-*O*-demethylation in human liver microsomes, with IC_{50} values of 0.17 μmol·L^{-1}, and 0.13 μmol·L^{-1}, respectively [51]. Psoralen and isopsoralen also displayed moderate inhibition of CYP2D6, with IC_{50} values of 3.59 μmol·L^{-1} and 9.51 μmol·L^{-1}, respectively [51]. In 2013, Zhuang *et al*. found that isopsoralen was a

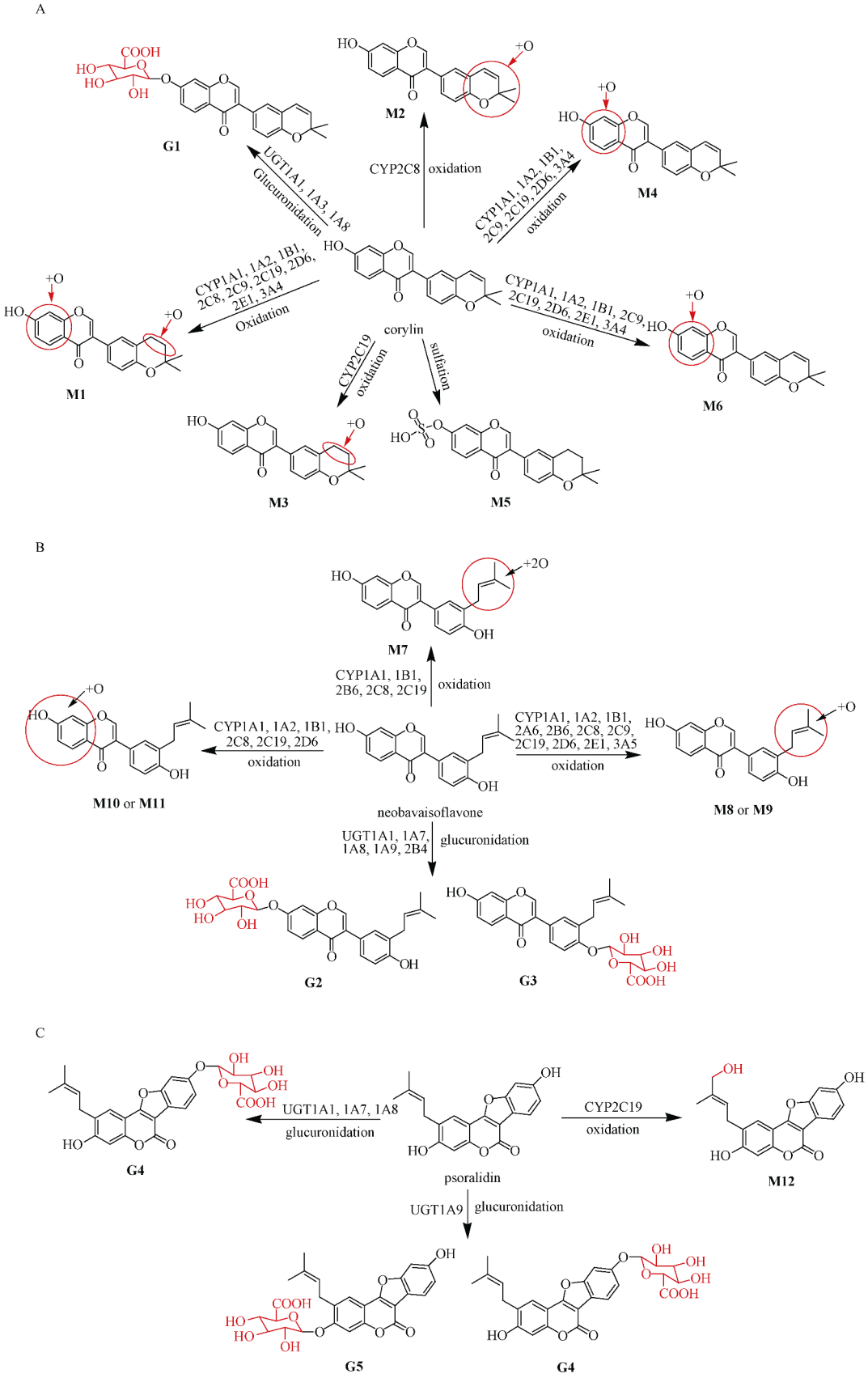


Fig. 3 The metabolic pathways of corylin (A), neobavaisoflavone (B) and psoralidin (C) in Psoraleae Fructus in human liver preparations

Table 1 Kinetic parameters of oxidative metabolism of the constituents in Psoraleae Fructus in HLM and recombinant CYPs

Compound	Enzyme source	Metabolite	K_m (μmol·L^{-1})	V_{max} (pmol·min^{-1}·mg^{-1})	CL_{int} (μL·min^{-1}·mg^{-1})	Ref.
Corylin	HLM	M1	1.57 ± 0.04	38.19 ± 0.24	24.29 ± 0.67	[29]
		M2	3.25 ± 0.20	38.80 ± 1.12	11.94 ± 0.80	[29]
		M4	1.85 ± 0.21	5.46 ± 0.26	2.95 ± 0.37	[29]
		M6	2.64 ± 0.14	5.37 ± 0.12	2.03 ± 0.11	[29]
	CYP1A1	M1	6.47 ± 0.85	165.90 ± 13.49	26.63 ± 3.96	[29]
		M4	12.11 ± 0.85	189.90 ± 9.61	15.68 ± 1.35	[29]
		M6	7.41 ± 1.01	48.97 ± 4.30	6.61 ± 1.07	[29]
	CYP1A2	M1	8.79 ± 0.73	60.51 ± 1.75	6.89 ± 0.60	[29]
		M4	10.50 ± 1.26	72.97 ± 3.22	6.94 ± 0.89	[29]
		M6	10.03 ± 1.15	36.19 ± 1.51	3.61 ± 0.44	[29]
	CYP1B1	M1	1.09 ± 0.06	36.10 ± 0.41	33.09 ± 1.78	[29]
		M4	5.48 ± 1.13	4.12 ± 0.49	0.75 ± 0.18	[29]
	CYP2C8	M1	1.31 ± 0.13	18.36 ± 0.40	14.05 ± 1.39	[29]
		M2	2.19 ± 0.23	15.1 ± 0.77	6.90 ± 0.81	[29]
	CYP2C9	M1	1.70 ± 0.21	10.03 ± 0.50	5.92 ± 0.80	[29]
		M6	1.38 ± 0.08	6.62 ± 0.08	4.79 ± 0.27	[29]
	CYP2C19	M1	4.44 ± 0.28	587.50 ± 11.09	132.41 ± 8.85	[29]
		M4	1.75 ± 0.22	25.14 ± 0.78	14.39 ± 1.90	[29]
	CYP2D6	M4	1.31 ± 0.10	6.35 ± 0.18	4.86 ± 0.38	[29]
Neobavaisoflavone	HLM	M8	5.41 ± 0.91	67.28 ± 3.68	12.43 ± 2.19	[30]
		M9	3.35 ± 0.48	33.60 ± 1.39	10.04 ± 1.49	[30]
		M10	4.64 ± 0.64	9.31 ± 0.40	2.01 ± 0.29	[30]
		M11	2.22 ± 0.16	15.53 ± 0.30	6.99 ± 0.53	[30]
	CYP1A1	M7	5.98 ± 0.78	30.63 ± 1.10	5.12 ± 0.67	[30]
		M8	2.62 ± 0.73	22.12 ± 3.13	8.43 ± 2.62	[30]
		M9	1.06 ± 0.20	32.29 ± 2.38	30.46 ± 6.09	[30]
		M10	3.72 ± 1.53	130.0 ± 32.38	34.96 ± 16.84	[30]
		M11	1.38 ± 0.29	26.1 ± 2.33	18.89 ± 4.29	[30]
	CYP1A2	M8	23.73 ± 1.72	36.27 ± 1.07	1.53 ± 0.12	[30]
		M9	20.44 ± 1.78	601.9 ± 20.48	29.45 ± 2.75	[30]
		M10	34.94 ± 2.81	266.6 ± 9.92	7.63 ± 0.68	[30]
		M11	24.02 ± 2.60	36.83 ± 1.63	1.53 ± 0.18	[30]
	CYP2C8	M9	9.25 ± 0.61	121.8 ± 2.51	13.16 ± 0.90	[30]
	CYP2C19	M8	14.38 ± 5.79	912.0 ± 276.0	63.42 ± 31.94	[30]
		M9	12.63 ± 2.82	197.5 ± 33.18	15.64 ± 4.37	[30]
		M10	39.66 ± 19.72	52.38 ± 20.68	1.32 ± 0.84	[30]
Psoralidin	HLM	--	5.171 ± 0.43	16.27 ± 1.21 (nmol·min^{-1}·pmol^{-1})	3.15 ± 0.22 (ml·min^{-1}·pmol^{-1})	[36]
	CYP2C19	M12	2.42 ± 0.15	3.01 ± 0.23 (nmol·min^{-1}·pmol^{-1})	1.24 ± 0.14 (ml·min^{-1}·pmol^{-1})	[36]

Table 2 Kinetic parameters of *O*-glucuronidation of the constituents in Psoraleae Fructus in HLM and recombinant UGTs

Compound	Enzyme source	Metabolite	K_m (μmol·L^{-1})	V_{max} (pmol·min^{-1}·mg^{-1})	CL_{int} (μL·min^{-1}·mg^{-1})	Ref.
Corylin	HLM	G1	5.27 ± 0.46	660.1 ± 31.75	125.33 ± 12.58	[29]
	UGT1A1	G1	3.20 ± 0.50	390.8 ± 29.15	122.32 ± 21.07	[29]
	UGT1A3	G1	3.83 ± 0.37	76.99 ± 3.80	20.11 ± 2.16	[29]
	UGT1A8	G1	25.59 ± 1.94	83.76 ± 3.06	3.27 ± 0.28	[29]

Continued

Compound	Enzyme source	Metabolite	K_m (μmol·L^{-1})	V_{max} (pmol·min^{-1}·mg^{-1})	CL_{int} (μL·min^{-1}·mg^{-1})	Ref.
Neobavaisoflavone	HLM	G2	6.58 ± 1.25	1788.0 ± 203.6	271.90 ± 60.39	[30]
		G3	1.41 ± 0.13	919.1 ± 20.23	651.38 ± 60.31	[30]
	UGT1A1	G2	3.64 ± 0.48	912.4 ± 49.36	250.87 ± 35.80	[30]
		G3	1.03 ± 0.11	48.33 ± 1.59	47.01 ± 5.35	[30]
	UGT1A7	G2	0.41 ± 0.06	11.93 ± 0.55	28.87 ± 4.57	[30]
		G3	0.31 ± 0.04	135.3 ± 4.36	438.15 ± 56.41	[30]
	UGT1A8	G2	4.52 ± 0.54	419.1 ± 18.69	92.68 ± 11.73	[30]
		G3	4.0 ± 0.51	147.0 ± 6.84	36.75 ± 5.00	[30]
	UGT1A9	G2	1.77 ± 0.14	70.01 ± 1.37	39.49 ± 3.11	[30]
		G3	0.75 ± 0.07	805.9 ± 17.46	1073.25 ± 108.93	[30]
Bakuchiol	HLM	--	4.08 ± 0.10	3.72 ± 0.17 (nmol·min^{-1}·mg^{-1})	0.91 ± 0.05 (mL·min^{-1}·mg^{-1})	[34]
	UGT1A1	--	4.41 ± 0.08	0.34 ± 0.02 (pmol·min^{-1}·mg^{-1})	0.05 ± 0.01 (mL·min^{-1}·mg^{-1})	[34]
	UGT1A3	--	10.05 ± 1.10	0.34 ± 0.02 (pmol·min^{-1}·mg^{-1})	0.02 ± 0.00 (mL·min^{-1}·mg^{-1})	[34]
	UGT2B15	--	3.50 ± 0.30	0.35 ± 0.05 (pmol·min^{-1}·mg^{-1})	0.07 ± 0.01 (mL·min^{-1}·mg^{-1})	[34]
Bavachinin	HLM	--	12.4 ± 0.6	629 ± 13	26.2	[35]
	UGT1A1	--	9.7 ± 0.6	606 ± 14	31.1	[35]
	UGT1A3	--	9.1 ± 1.2	35.4 ± 2.1	3.9	[35]
	UGT1A8	--	2.3 ± 0.2	954 ± 33	216.2	[35]

Table 3 Pharmacokinetic parameters of the major constituents in Psoraleae Fructus in rat plasma after oral administration or intravenous administration of single compound or Psoraleae Fructus extract

Compound	Mode of administration	Dose	$T_{1/2}$ /h	C_{max} (μg·mL^{-1})	T_{max} /h	AUC_{0-t} (μg·h·mL^{-1})	$AUC_{0-\infty}$ (μg·h·mL^{-1})	CL (L·h^{-1}·kg^{-1})	Ref.
Bavachinin	p.o.	70 mg·kg^{-1}	2.27 ± 1.63	0.16 ± 0.060	0.68 ± 0.21	0.70 ± 0.18	0.76 ± 0.19	--	[44]
Bavachinin	i.v.	5 mg·kg^{-1}	0.64 ± 0.28	--	--	0.95 ± 0.38	0.96 ± 0.38	5.76 ± 1.75	[44]
Psoralenoside*	p.o.	3.87 g·kg^{-1}	3.49 ± 0.45	1.46 ± 0.24	2.58 ± 0.59	12.01 ± 2.47	12.10 ± 2.49	4.39 ± 1.02	[45]
Isopsoralenoside*	p.o.	3.87 g·kg^{-1}	5.64 ± 3.13	2.58 ± 1.60	2.58 ± 0.59	16.82 ± 6.45	17.21 ± 6.46	2.56 ± 0.88	[45]
Psoralen*	p.o.	3.87 g·kg^{-1}	2.67 ± 0.65	3.97 ± 1.26	9.00 ± 1.67	41.14 ± 16.20	41.31 ± 16.13	0.02 ± 0.01	[45]
Isopsoralen*	p.o.	3.87 g·kg^{-1}	2.97 ± 0.87	2.13 ± 0.82	10.00 ± 1.27	25.31 ± 9.40	25.46 ± 9.40	0.02 ± 0.01	[45]

Note: The * indicates that the rats was orally administered with Psoraleae Fructus extract

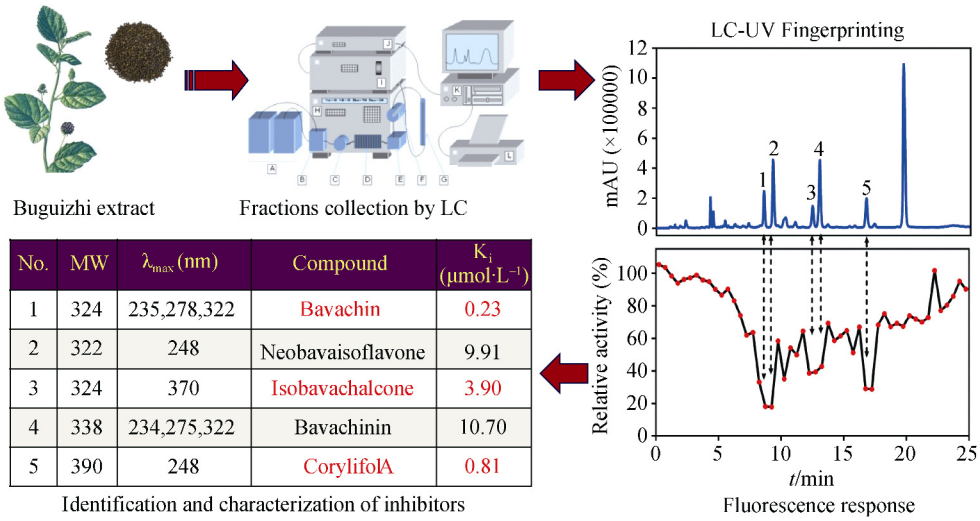
Table 4 Inhibition of human CYPs by the major constituents in Psoraleae Fructus

Constituent	Target Enzyme	Enzyme source	Probe reaction	IC_{50} (μmol·L^{-1})	K_i (μmol·L^{-1})	Inhibition mode	Ref.
Psoralen	CYP1A2	HLM	Phenacetin-*O*-demethylation	0.17	--	--	[51]
	CYP2D6	HLM	Dextromethorphan-*O*-demethylation	3.59	--	--	[51]
	CYP1A2	HLM	Phenacetin-*O*-demethylation	0.26	--	--	[52]
	CYP2D6	HLM	Dextromethorphan-*O*-demethylation	3.6	--	--	[52]
Isopsoralen	CYP1A2	HLM	Phenacetin-*O*-demethylation	0.13	--	--	[51]
	CYP2D6	HLM	Dextromethorphan-*O*-demethylation	9.51	--	--	[51]
	CYP1A2	HLM	Phenacetin-*O*-demethylation	0.22	0.4 (K_I)	TDI	[52]
	CYP2D6	HLM	Dextromethorphan-*O*-demethylation	8.49	--	--	[52]
Psoraleae Fructus extract	CYP3A4	CYP3A4	Luciferin-IPA-*O*-demethylation	6.0 (μg·mL^{-1})	--	--	[53]
Bakuchicin	CYP1A1	HLM	Phenacetin-*O*-demethylation	--	0.11	Competitive	[54]
	CYP1A2	HLM	Phenacetin-*O*-demethylation	--	0.32	Competitive	[54]
Psoralidin	CYP1A2	HLM	Phenacetin-*O*-demethylation	1.8	1.2	Noncompetitive	[55]
	CYP2C8	HLM	Paclitaxel-6α-hydroxylation	0.3	0.3	Noncompetitive	[55]
Genistein	CYP2A6	CYP2A6	Midazolam-1′-hydroxylation	6.0	1.3	Noncompetitive	[58]
Daidzein	CYP2A6	CYP2A6	Midazolam-1′-hydroxylation	27.0	0.7	Noncompetitive	[58]

time-dependent inhibitor of CYP1A2, with k_{inact} and K_I values of 0.050 min^{-1} and 0.40 μmol·L^{-1}, respectively [52]. They also found that psoralen and isopsoralen were moderate inhibitors of CYP2D6, with IC_{50} values of 3.60 μmol·L^{-1} and 8.49 μmol·L^{-1}, respectively (Table 4) [52]. Liu and Flynn *et al*. found that a methanol–water extract of the fruits of Psoraleae Fructus and its major constituents (psoralen and isopsoralen) could inhibit human CYP3A4 as a recombinant enzyme and in HuH-7 cells, with an IC_{50} value of 6.0 μg·mL^{-1} for Psoraleae Fructus extract [53]. In 2016 Sun *et al*. investigated the inhibitory potential of bakuchicin for human CYP1A1 and CYP1A2 using recombinant enzymes as the enzyme source. The results demonstrated that bakuchicin potently inhibited CYP1A-mediated phenacetin-*O*-deethylation by recombinant human CYP1A1 and CYP1A2, with values of 0.11 μmol·L^{-1} and 0.32 μmol·L^{-1} for CYP1A1 and CYP1A2, respectively [54]. This finding suggested that bakuchicin was more effective against CYP1A1-mediated biotransformation than that of CYP1A2. Psoralidin could also inhibit the catalytic activities of CYP1A2 and CYP2C8 in a dose-dependent manner, with calculated IC_{50} values of 1.8 μmol·L^{-1}, and 0.3 μmol·L^{-1}, respectively [55]. Further investigation demonstrated that psoralidin functioned as a noncompetitive inhibitor of both CYP1A2 and CYP2C8, with K_i values of 1.2 μmol·L^{-1} and 0.3 μmol·L^{-1}, respectively [55]. In addition, several groups found that genistein and daidzein, also present in Psoraleae Fructus, displayed strong inhibition of CYP2A6, with K_i values of 1.3 μmol·L^{-1} and 0.7 μmol·L^{-1} for genistein and daidzein, respectively, but these two natural products displayed weak inhibition of CYP3A and moderate inhibition of CYP2C9 [56-58].

UGT inhibition by Psoraleae Fructus and its constituents

Wang *et al*. reported that both the ethanol extract of Psoraleae Fructus and some of its fractions displayed strong inhibition of human UDP-glucuronosyltransferase 1A1 (UGT1A1), a key conjugative enzyme responsible for the metabolic elimination and detoxification of a range of therapeutic drugs and endogenous toxins (such as bilirubin) [59]. With the help of newly developed fluorogenic probes for human UGT1A1 [60], the Ge group identified five major constituents (including bavachin, neobavaisoflavone, isobavachalcone, bavachinin and corylifol A) as natural inhibitors of UGT1A1 [61] by comparison of chemical fingerprints and inhibition profiles for LC fractions of Psoraleae Fructus extract (Fig. 4). These findings demonstrated that at least five major constituents could affect the detoxification ability of UGT1A1, which partially explained why the seeds of *P. corylifolia* could trigger hyperbilirubinemia and liver injury [62-63]. In addition, these findings suggested that Psoraleae Fructus and its major constituents may trigger herb-endobiotic interactions (HEI) *via* inhibition of UGT1A1 or other enzymes participating in metabolism of endogenous compounds.



No.	MW	λ_{max} (nm)	Compound	K_i (μmol·L^{-1})
1	324	235,278,322	Bavachin	0.23
2	322	248	Neobavaisoflavone	9.91
3	324	370	Isobavachalcone	3.90
4	338	234,275,322	Bavachinin	10.70
5	390	248	CorylifolA	0.81

Identification and characterization of inhibitors

Fluorescence response

Fig. 4 Identification of natural UGT1A1 inhibitors guided by chemical fingerprinting combined with a fluorescence-based inhibition assay

Li *et al*. found that corylin only weakly inhibited human UGTs, but psoralidin, coryfolin, bavachinin and neobavaisoflavone demonstrated differential inhibitory effects on various human UGTs [64]. The results are listed in Table 5. Another study found that psoralidin could inhibit UGT1A1 and UGT1A7, with IC_{50} values of 6.1, and 0.4 μmol·L^{-1}, respectively [55]. Further inhibition kinetic analyses showed that psoralidin was a noncompetitive inhibitor of both UGT1A1 and UGT1A7, with K_i values of 5.6 and 0.3 μmol·L^{-1}, respectively [55]. Zhang *et al*. reported that psoralidin could competitively inhibit UGT1A1-mediated SN-38 *O*-glucuronidation in recombinant human UGT1A1, with a K_i value of 5.8 μmol·L^{-1} [65]. In 2014, Shan *et al*. compared the inhibitory effects of bavachalcone and corylin on UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A10, and UGT2B4, using 4-methylumbelliferone (4-MU) as a nonspecific substrate. The results demonstrated that bavachalcone exhibited strong to moderate inhibition of UGT1A1 and UGT1A7, with IC_{50}

values of 11.3 and 3.6 μmol·L^{-1} for UGT1A1 and UGT1A7, respectively [66]. Furthermore, bavachalcone was validated as a noncompetitive inhibitor against both UGT1A1 and UGT1A7, with K_i values of 5.41 and 4.51 μmol·L^{-1}, respectively [66].

CES inhibition by Psoraleae Fructus and its constituents

Over the past two decades, two major carboxylesterase (CES) isozymes, including human CES1 (hCES1A) and human CES2 (hCES2A), have been identified and extensively investigated [67]. Sun *et al*. investigated the inhibitory effects of the major constituents in Psoraleae Fructus on human CES1A using HLMs as the enzyme source. The results showed that neobavaisoflavone, corylifolinin, coryfolin, corylin, psoralen, and bavachinin could strongly inhibit human CES1A, with K_i values ranged from 0.5 to 9.4 μmol·L^{-1} [68]. Li *et al*. found that the ethanol extract of Psoraleae Fructus could strongly inhibit human CES2A, and then identified five natural constituents (neobovaisoflavone, isobavachalcone, bavachinin, corylifol A and bakuchiol) in this herb that were naturally occurring inhibitors of human CES2A with the help of chemical fingerprinting analysis combined with the CES2A inhibition assay [60]. The IC_{50} values of neobovaisoflavone, isobavachalcone, bavachinin, corylifol A and bakuchiol against human CES2A were evaluated as 6.39, 2.85, 4.31, 0.87 and 7.28 μmol·L^{-1}, respectively. Further investigations demonstrated that these five constitutes are noncompetitive inhibitors of CES2A-mediated FD hydrolysis (Table 6).

Table 5 Inhibition of human UGTs by Psoraleae Fructus and its major constituents

Constituent	Target Enzyme	Enzyme source	Probe reaction	IC_{50} (μmol·L^{-1})	K_i (μmol·L^{-1})	Inhibition mode	Ref.
Psoralidin	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	6.1	5.6	Noncompetitive	[55]
	UGT1A7	UGT1A7	4-MU-*O*-glucuronidation	0.4	0.3	Noncompetitive	[55]
Psoraleae Fructus extract	UGT1A1	HLM	NCHN-*O*-glucuronidation	12.5 μg·mL^{-1}	--	--	[61]
Bavachin	UGT1A1	HLM	NCHN-*O*-glucuronidation	1.9	1.2	Noncompetitive	[61]
	UGT1A1	UGT1A1	NCHN-*O*-glucuronidation	0.8	0.04	Noncompetitive	[61]
	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	1.8	1.1	Competitive	[61]
Neobavaisoflavone	UGT1A1	HLM	NCHN-*O*-glucuronidation	2.4	9.9	Noncompetitive	[61]
	UGT1A1	UGT1A1	NCHN-*O*-glucuronidation	2.3	4.0	Noncompetitive	[61]
	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	1.8	12.0	Competitive	[61]
Isobavachalcone	UGT1A1	HLM	NCHN-*O*-glucuronidation	4.43	4.13	Noncompetitive	[61]
	UGT1A1	UGT1A1	NCHN-*O*-glucuronidation	3.40	4.09	Noncompetitive	[61]
	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	13.04	10.93	Competitive	[61]
Bavachinin	UGT1A1	HLM	NCHN-*O*-glucuronidation	4.16	7.89	Noncompetitive	[61]
	UGT1A1	UGT1A1	NCHN-*O*-glucuronidation	1.27	4.09	Noncompetitive	[61]
	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	1.99	2.22	Competitive	[61]
Corylifol A	UGT1A1	HLM	NCHN-*O*-glucuronidation	1.48	1.46	Noncompetitive	[61]
	UGT1A1	UGT1A1	NCHN-*O*-glucuronidation	0.65	0.79	Noncompetitive	[61]
	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	1.48	0.47	Competitive	[61]
Coryfolin	UGT1A6	UGT1A6	4-MU-*O*-glucuronidation	20.3	10.6	Noncompetitive	[64]
	UGT1A7	UGT1A7	4-MU-*O*-glucuronidation	1.5	1.5	Noncompetitive	[64]
	UGT1A9	UGT1A9	4-MU-*O*-glucuronidation	1.4	0.6	Noncompetitive	[64]
	UGT2B4	UGT2B4	4-MU-*O*-glucuronidation	26.6	--	--	[64]
	UGT2B7	UGT2B7	4-MU-*O*-glucuronidation	7.7	27.2	Noncompetitive	[64]
Bavachinin	UGT1A7	UGT1A7	4-MU-*O*-glucuronidation	3.2	3.2	Noncompetitive	[64]
	UGT1A8	UGT1A8	4-MU-*O*-glucuronidation	24.9	--	--	[64]
	UGT1A9	UGT1A9	4-MU-*O*-glucuronidation	0.1	0.2	Noncompetitive	[64]
	UGT2B7	UGT2B7	4-MU-*O*-glucuronidation	18.2	9.4	Noncompetitive	[64]
Neobavaisoflavone	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	3.6	--	--	[64]
	UGT1A6	UGT1A6	4-MU-*O*-glucuronidation	21.6	3.3	Noncompetitive	[64]
	UGT1A7	UGT1A7	4-MU-*O*-glucuronidation	0.2	0.2	Competitive	[64]
	UGT1A8	UGT1A8	4-MU-*O*-glucuronidation	11.5	0.01	Noncompetitive	[64]
	UGT1A9	UGT1A9	4-MU-*O*-glucuronidation	0.02	0.3	Competitive	[64]
	UGT2B4	UGT2B4	4-MU-*O*-glucuronidation	3.6	12.8	Competitive	[64]
Bavachalcone	UGT1A1	UGT1A1	4-MU-*O*-glucuronidation	11.3	5.4	Noncompetitive	[66]
	UGT1A7	UGT1A7	4-MU-*O*-glucuronidation	3.6	4.5	Noncompetitive	[66]

Table 6 Inhibition of human CESs by the constituents in Psoraleae Fructus

Constituent	Target Enzyme	Enzyme source	Probe reaction	IC_{50} ($\mu g \cdot mL^{-1}$)	K_i ($\mu g \cdot mL^{-1}$)	Inhibition mode	Ref.
Neobavaisoflavone	CES1A	HLM	BMBT-hydrolysis	--	5.3	Noncompetitive	[67]
Corylifolinin	CES1A	HLM	BMBT-hydrolysis	--	9.4	Noncompetitive	[67]
Coryfolin	CES1A	HLM	BMBT-hydrolysis	--	1.9	Noncompetitive	[67]
Corylin	CES1A	HLM	BMBT-hydrolysis	--	0.7	Noncompetitive	[67]
Bavachinin	CES1A	HLM	BMBT-hydrolysis	--	0.5	Competitive	[67]
Neobavaisoflavone	CES2A	HLM	FD-hydrolysis	6.39	3.89	Noncompetitive	[69]
Isobavachalcone	CES2A	HLM	FD-hydrolysis	2.85	1.61	Noncompetitive	[69]
Bavachinin	CES2A	HLM	FD-hydrolysis	4.31	1.12	Noncompetitive	[69]
Corylifol A	CES2A	HLM	FD-hydrolysis	0.87	0.62	Noncompetitive	[69]
Bakuchiol	CES2A	HLM	FD-hydrolysis	7.28	2.12	Noncompetitive	[69]

The K_i values of neobavaisoflavone, isobavachalcone, bavachinin, corylifol A, and bakuchiol were also evaluated as 3.89, 1.64, 1.12, 0.62 and 2.12 $\mu mol \cdot L^{-1}$, respectively [69]. These findings suggested that both the ethanol extract of Psoraleae Fructus and its major constituents could strongly inhibit human CES, implying that Psoraleae Fructus could be used for modulating the pharmacokinetic behavior of hCES-substrate drugs and alleviating CES2A- associated drug toxicity [70-71].

Induction of drug-metabolizing enzymes by the constituents in Psoraleae Fructus

In contrast to the extensive studies on the inhibition of drug-metabolizing enzymes by the constituents of Psoraleae Fructus, only a few studies have been conducted to explore the inductive effects of Psoraleae Fructus constituents on human drug-metabolizing enzymes, and most of these studies were focused on the regulation of human CYPs. Li *et al*. reported that psoralen, isopsoralen, isobavachalcone and bavachin could activate the constitutive androstane receptor (CAR) and induce the expression of CYP2B6 (Table 7) [72]. Wang *et al*. reported that 6-prenylnarigenin (6-PN), one of the bioactive compounds in Psoraleae Fructus, could induce CYP1A1 and CYP1B1 in both MCF-7 and MCF-10A cell lines [73]. They also found that 6-PN was an AhR agonist. These findings suggested that 6-PN could enhance the nontoxic estrogen 2-hydroxylation pathway through AhR mediated up-regulation of CYP1A1 [73]. Baumgart *et al*. investigated the inductive effects of four furocoumarins (angelicin, bergamottin, isopimpinellin, and 8-methoxypsoralen) in Buguizhi with regard to both the expression and activity of aryl hydrocarbon receptor (AhR)-regulated CYP1A1 in rat hepatocytes, in the presence or absence of light [74]. The results showed that 8-methoxypsoralen and angelicin led to a significant induction of CYP1A1 mRNA in hepatocytes, while all furocoumarins except bergamottin increased xenobiotic-responsive element-driven reporter gene expression in transfected H4IIE rat hepatoma cells when light was excluded.

Table 7 Induction of the constituents in Psoraleae Fructus on human drug metabolizing enzymes

Compound	Living system	Dose ($\mu mol \cdot L^{-1}$)	Target Enzyme	Inductive efficacy (n-fold of control, mRNA)	Ref.
Psoralen	LS174T	20	CYP2B6	3.0	[72]
Isopsoralen	LS174T	20	CYP2B6	2.9	[72]
Isobavachalcone	LS174T	20	CYP2B6	2.0	[72]
Bavachin	LS174T	20	CYP2B6	2.9	[72]
6-prenylnarigenin	MCF-10A MCF-7	1	CYP1A1	16 290	[73]
6-prenylnarigenin	MCF-10A MCF-7	1	CYP1B1	2.0 25	[73]
8-methoxypsoralen	Primary rat hepatocytes	1000	CYP1A1	6.6	[74]
Psoralen	Hepa1c1c7	20 $\mu g \cdot mL^{-1}$	QR	1.9 *	[76]
Daidzin	PC12	4	AChE	> 2	[77]
Bavachalcone	HUVECs	5	MnSOD	1.5	[78]

Note: The * indicates that the change of protein level of QR by Psoralen

In addition to the induction of CYPs by the constituents in Psoraleae Fructus, some groups also investigated the inductive effects of Psoraleae Fructus constituents on other enzymes in the human body. Quinone reductase (QR), a key enzyme participating in metabolism of mutagens and carcinogens, could be induced by a crude extract from the seeds

of *P. corylifolia* and its major constituents. Lee, S.J found that the ethyl acetate-soluble fraction of the methanolic extract from Psoraleae Fructus could induce QR in a Hepa 1c1c7 murine hepatoma cell line at the dosage of 1.2 μg·mL^{-1} [75]. Further investigation demonstrated that psoralen was a naturally occurring QR inducer in Psoraleae Fructus, and this compound could induce QR activities about 1.5-fold at a dosage of 14.8 μg·mL^{-1} [76]. These finding implied that Psoraleae Fructus and psoralen hold the potentials for blocking the initiation and/or promotion stage of carcinogenesis *via* induction of QR. Liu *et al*. demonstrated that daidzin, a natural flavonoid in Psoraleae Fructus, could induce the expression and the activity of acetyl cholinesterase (AChE) *via* targeting GPR30 in cultured PC12 cells [77]. This finding implied that daidzin could be used as a drug candidate for the treatment of brain diseases by modulating the expression and function of AChE. Dang *et al*. examined the inductive effect of bavachalcone on manganese superoxide dismutase (MnSOD) expression and explored whether this effect was mediated through the AMP-activated protein kinase (AMPK) signaling pathway [78]. The results demonstrated that bavachalcone could protect endothelial function by increasing AMPK activity and MnSOD expression, thereby reducing mitochondrial oxidative stress.

Conclusions and Future Perspectives

In summary, this review discusses the metabolic interactions between Psoraleae Fructus constituents and human drug-metabolizing enzymes (DMEs), an important class of enzymes participating in drug disposition and endogenous metabolism. The metabolic pathways and pharmacokinetic parameters of the major constituents from Chinese herb Psoraleae Fructus, along with their chemical structures are summarized, which will be very helpful for pharmacologists to gain greater understanding of the metabolic fates of Psoraleae Fructus constituents in both human and experimental animals. Meanwhile, recent advances in the modulatory effects of the major constituents in Psoraleae Fructus on human DMEs, including human cytochrome P450 enzymes (CYPs), UDP-glucuronosyltransferases (UGTs) and esterases, have also been summarized. The information presented in this review will facilitate the rational use of the Chinese herb Psoraleae Fructus in clinical settings, and especially to avoid potential risks of HDI or HEI as a result of modulation of human DME activity.

Accumulative evidence has indicated that most Psoraleae Fructus constituents can be rapidly absorbed into the circulatory system and the majority of these constituents can strongly interact with human DMEs. However, most of the investigations on inhibition of human DMEs by Psoraleae Fructus constituents have been conducted *in vitro*, while the inductive effects of the major constituents in Psoraleae Fructus on human DMEs have not been well-investigated. In view of that Psoraleae Fructus or Psoraleae Fructus-related products are frequently used in combination with therapeutic drugs in clinical settings, and it is necessary to carefully investigate the modulatory effects of Psoraleae Fructus-related products and its major constituents on human drug metabolizing enzymes, as well as to evaluate their influence on the pharmacokinetic behaviors of co-administrated drug(s) *in vivo*. In future, more in-depth studies including pharmacological and toxicological assays of each constituent in Psoraleae Fructus, the roles of drug-metabolizing enzymes in the detoxification or activation of Psoraleae Fructus constituents, the ability of Psoraleae Fructus constituents to modulate the activity of human drug-metabolizing enzymes *in vivo*, the underlying molecular mechanism of Psoraleae Fructus constituents to regulate human DMEs, the clinical assessment of the beneficial or unbeneficial effects of Psoraleae Fructus co-administrated with therapeutic drug(s), should be conducted. All these investigations will aid clinicians to avoid the occurrence of HDI or other side effects in clinical settings [79]. To make Psoraleae Fructus-related products safer and more effective, those constituents that bring undesirable effects (such as toxic effects or trigger HDI) could be strictly restricted within tolerable limits [80-83].

References

[1] Koul B, Taak P, Kumar A, *et al*. Genus *Psoralea*: a review of the traditional and modern uses, phytochemistry and pharmacology [J]. *J Ethnopharmacol*, 2019, **232**: 201-226.

[2] Chopra B, Dhingra AK, Dhar KL. *Psoralea corylifolia* (Buguzhi)-folklore to modern evidence: review [J]. *Fitoterapia*, 2013, **90**: 44-56.

[3] Zhang X, Zhao W, Wang Y, *et al*. The chemical constituents and bioactivities of *Psoralea corylifolia*: a review [J]. *Am J Chin Med*, 2016, **44**(1): 35-60.

[4] 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 Med*, 2019, **19**(1): 84.

[5] Clairet AL, Boiteux-Jurain M, Curtit Elsa, *et al*. Interaction between phytotherapy and oral anticancer agents: prospective study and literature review [J]. *Med Oncol*, 2019, **36**(5): 45.

[6] Alam F, Khan GN, Asad MHHB. *Psoralea corylifolia*: ethnobotanical, biological, and chemical aspects: a review [J]. *Phytother Res*, 2018, **32**(4): 597-615.

[7] Zhao LH, Huang CY, Shan Z, *et al*. Fingerprint analysis of *Psoralea corylifolia* by HPLC and LC-MS [J]. *Chromatogr B Analyt Technol Biomed Life Sci*, 2005, **821**(1): 67-74.

[8] Zhang YM, Chen ZY, Xu XK, *et al*. Rapid separation and simultaneous quantitative determination of 13 constituents in Psoraleae Fructus by a single marker using high-performance liquid chromatography with diode array detection [J]. *J Sep Sci*, 2017, **40**(21): 4191-4202.

[9] Chen CH, Hwang TL, Chen LC, *et al*. Isoflavones and anti-inflammatory constituents from the fruits of *Psoralea corylifolia* [J]. *Phytochemistry*, 2017, **143**: 186-193.

[10] Yin S, Fan CQ, Wang Y, *et al*. Antibacterial prenylflavone derivatives from *Psoralea corylifolia*, and their structure-activity relationship study [J]. *Bioorg Med Chem*, 2004, **12**(16): 4387-4392.

[11] Haraguchi H, Inoue J, Tamura Y, *et al*. Antioxidative components of *Psoralea corylifolia* (Leguminosae) [J]. *Phytother Res*, 2002, **16**(6): 539-544.

[12] Wang Y, Hong CT, Zhou CG, *et al*. Screening antitumor compounds psoralen and isopsoralen from *Psoralea corylifolia*

seeds [J]. *Evid Based Complement Alternat Med*, 2011, **2011**: 363052.
[13] Sun DX, Ge GB, Dong PP, *et al*. Inhibition behavior of fructus psoraleae's ingredients towards human carboxylesterase 1 (hCES1) [J]. *Xenobiotica*, 2016, **46**(6): 503-510.
[14] Li YG, Hou J, Li SY, *et al*. Fructus Psoraleae contains natural compounds with potent inhibitory effects towards human carboxylesterase 2 [J]. *Fitoterapia* , 2015, **101**: 99-106.
[15] Zhao H, Chen Z. Screening of neuraminidase inhibitors from traditional Chinese medicines by integrating capillary electrophoresis with immobilized enzyme microreactor [J]. *J Chromatogr A*, 2014, **1340**: 139-145.
[16] Choi JH, Rho MC, Lee SW, *et al*. Bavachin and isobavachalcone, acyl-coenzyme A: Cholesterol acyltransferase inhibitors from *Psoralea corylifolia* [J]. *Arch Pharm Res*, 2008, **31**(11): 1419-1423.
[17] Khatune NA, Islam ME, Haque ME, *et al*. Antibacterial compounds from the seeds of *Psoralea corylifolia* [J]. *Fitoterapia*, 2004, **75**(2): 228-230.
[18] Lee SJ, Nam KW, Mar W. Effects of psoralen from *Psoralea corylifolia* on quinone reductase, ornithine decarboxylase, and JB6 cells transformation promotion [J]. *Arch Pharm Res*, 2011, **34**(1): 31-36.
[19] Wang YC, Hong C, Zhou D, *et al*. Screening antitumor compounds psoralen and isopsoralen from *Psoralea corylifolia* Seeds [J]. *Evid-Based Compl Alt*, 2011, **2011**: 363052.
[20] Xiao GG, Li L, Chen Z, *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**(34): 5470-5476.
[21] Chen Y, Cheung YT, Kong LD, *et al*. Transcriptional regulation of corticotrophin releasing factor gene by furocoumarins isolated from seeds of *Psoralea corylifolia* [J]. *Life Sci*, 2008, **82**(21-22): 1117-1121.
[22] Lu HL, Zhang D, Liu P, *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**(3): 641-647.
[23] Mehta G, Nayak UR, Dev S. Meroterpenoids-I: *Psoralea corylifolia* Bakuchiol, a novel monoterpene phenol [J]. *Tetrahedron*, 1973, **29**: 1119-1125.
[24] Katsura H, Tsukiyama RI, Suzuki A, *et al*. *In vitro* antimicrobial activities of bakuchiol against oral microorganisms [J]. *Antimicrob Agents Ch*, 2001, **45**(11): 3009-3013.
[25] Lim SH, Ha TY, Kim SR, *et al*. Ethanol extract of *Psoralea corylifolia* and its main constituent, bakuchiol, reduce bone loss in ovariectomised Sprague-Dawley rats [J]. *Br J Nutr*, 2009, **101**(7): 1031-1039.
[26] Bapat K, Chintalwar GJ, Pandey U, *et al*. Preparation and *in vitro* evaluation of radioiodinated bakuchiol as an anti-tumor agent [J]. *Appl Radiat Isot*, 2005, **62**(3): 389-393.
[27] Cho H, Jun JY, Song EK, *et al*. Bakuchiol: a hepatoprotective compound of *Psoralea corylifolia* on tacrine-induced cytotoxicity in Hep G2 cells [J]. *Planta Med*, 2001, **67**(8): 750-751.
[28] Shah CC, Bhalla VK, Dev S. Meroterpenoids-V: *Psoralea corylifolia*-4. 2, 3-epox-ybakuchiol, Delta (1), 3-hydroxybakuchiol, and Delta (3), 2-hydroxybakuchiol [J]. *J Indian Chem Soc*, 1997, **74**: 970-973.
[29] Qin Z, Li S, Yao Z, *et al*. Metabolic profiling of corylin *in vivo* and *in vitro* [J]. *J Pharm Biomed Anal*, 2018, **155**: 157-168.
[30] Xu J, Li M, Yao Z, *et al*. *In vitro* metabolic mapping of neobavaisoflavone in human cytochromes P450 and UDP-glucuronosyltransferase enzymes by ultra high-performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry [J]. *J Pharm Biomed Anal*, 2018, **158**: 351-360.
[31] Hu XJ, Zhang YB, Zhao ZJ, *et al*. Metabolic detoxification of bakuchiol is mediated by oxidation of CYP 450s in liver microsomes [J]. *Food Chem Toxicol*, 2018, **111**: 385-392.
[32] Chi M, Peng Y, Zheng J. Characterization of glutathione conjugates derived from reactive metabolites of bakuchiol [J]. *Chem Biol Interact*, 2016, **244**: 178-186.
[33] Jiao SY, Ai CH, Li AF, *et al*. *In vitro* inter-species comparison of metabolism and metabolic detoxifification of bakuchiol in liver microsomes [J]. *Chin Pharmacol Bull*, 2011, **27**: 216-220.
[34] Li F, Wang S, Lu D, *et al*. Identification of UDP-glucuronosyltransferases 1A1, 1A3 and 2B15 as the main contributors to glucuronidation of bakuchiol, a natural biologically active compound [J]. *Xenobiotica*, 2017, **47**(5): 369-375.
[35] Lv X, Hou J, Xia YL, *et al*. Glucuronidation of bavachinin by human tissues and expressed UGT enzymes: identification of UGT1A1 and UGT1A8 as the major contributing enzymes [J]. *Drug Metab Pharmacok*, 2015, **30**(5): 358-365.
[36] Shi X, Zhang G, Mackie B, *et al*. Comparison of the *in vitro* metabolism of psoralidin among different species and characterization of its inhibitory effect against UDP-glucuronosyltransferase (UGT) or cytochrome p450 (CYP450) enzymes [J]. *J Chromatogr B*, 2016, **1029**: 145-156.
[37] Sun H, Ma Z, Lu D, *et al*. Regio-and isoform-specific glucuronidation of psoralidin: evaluation of 3-o-glucuronidation as a functional marker for UGT1A9 [J]. *J Pharm Sci*, 2015, **104**(7): 2369-2377.
[38] Yang A, Chen J, Ma Y, *et al*. Studies on the metabolites difference of psoralen/isopsoralen in human and six mammalian liver microsomes *in vitro* by UHPLC-MS/MS [J]. *J Pharmaceut Biomed*, 2017, **141**: 200-209.
[39] Xie F, Du G, Ma S, *et al*. Structural elucidation of *in vitro* metabolites of bavachinin in rat liver microsomes by LC-ESI-MS^n and chemical synthesis [J]. *Xenobiotica*, 2016, **46**(4): 296-306.
[40] Wang PL, Yao ZH, Zhang FX, *et al*. Identification of metabolites of Psoraleae Fructus in rats by ultra-performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry analysis [J]. *J Pharm Biomed Anal*, 2015, **112**: 23-35.
[41] Su S, Wang Y, Bai L, *et al*. Structural elucidation of *in vivo* metabolites of isobavachalcone in rat by LC-ESI-MS^n and LC-NMR [J]. *J Pharm Biomed Anal*, 2015, **104**: 38-46.
[42] Hu C, Liang Q, Tang X, *et al*. *In vivo* metabolite identification of bakuchiol in rats by UPLC/ESI-PDA-QTOF-MS [J]. *Fitoterapia*, 2015, **106**: 129-134.
[43] Wang PL, Zhang FX, Qiu ZC, *et al*. Isolation and identification of metabolites of bakuchiol in rats [J]. *Fitoterapia*, 2016, **109**: 31-38.
[44] Qian J, Xie F, Shi Y, *et al*. Pharmacokinetic and metabolism studies of bavachinin through ultra-high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry [J]. *Biomed Chromatoqr*, 2018, **32**(10): e4293.
[45] 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**(1): 609-617.
[46] Li A, Ma N, Zhao Z, *et al*. Glycyrrhetinic acid might increase the nephrotoxicity of bakuchiol by inhibiting cytochrome P450 isoenzymes [J]. *Peer J*, 2016, **4**(9): e2723.
[47] Manikandan P, Naqini S. Cytochrome P450 structure, function and clinical significance: a review [J]. *Curr Drug Targets*, 2018, **19**(1): 38-54.
[48] Lv X, Zhang JB, Hou J, *et al*. Chemical probes for human UDP-Glucuronosyltransferases: a comprehensive review [J].

Biotechnol J, 2019, **14**(1): e1800002.
[49] Weng ZM, Ge GB, Dou TY, *et al*. Characterization and structure-activity relationship studies of flavonoids as inhibitors against human carboxylesterase 2 [J]. *Bioorganic Chemistry*, 2018, **77**: 320-329.
[50] Liu ZF. Effect of coumarin compounds on human CYP enzyme activity [D]. Hunan, Central South University, 2009.
[51] Zhong YH, Shen GL, Yuan M, *et al*. Inhibition and induction of cytochrome P450 enzyme activity by psoralen and isopsoralen [J]. *Chin J Pharmacol Toxicol*, 2012, **26** (4): 522-528.
[52] Zhuang XM, Zhong YH, Xiao WB, *et al*. Identification and characterization of psoralen and isopsoralen as potent CYP1A2 reversible and time-dependent inhibitors in human and rat preclinical studies [J]. *Drug Metab Dispos*, 2013, **41**(11): 1914-1922.
[53] 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]. *Toxicology Reports*, 2015, **2**: 530-534.
[54] Sun JK, Heung CO, Kim YC, *et al*. Selective inhibition of bakuchicin isolated from *Psoralea corylifolia* on CYP1A in human liver microsomes [J]. *Evid Based Complement Alternat Med*, 2016, **1**: 1-7.
[55] Shi XB, Zhang G, Mackie B, *et al*. Comparison of the *in vitro* metabolism of psoralidin among different species and characterization of its inhibitory effect against UDP-glucuronosyltransferase (UGT) or cytochrome P450 (CYP450) enzymes [J]. 2016, **1029-1030**: 145-156.
[56] Foster BC, Vandenhoek S, Hana J, *et al*. *In vitro* inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products [J]. *Phytomedicine*, 2003, **10**(4): 334-342.
[57] Michaela KZ, Kristyna K, Pavel A, *et al*. Interaction of isoflavonoids with human liver microsomal cytochromes P450: inhibition of CYP enzyme activities [J]. *Xenobiotica*, 2017, **47**(4): 324-331.
[58] Nakajima M, Itoh M, Yamanaka H, *et al*. Isoflavones inhibit nicotine c-oxidation catalyzed by human CYP2A6 [J]. *J Clin Pharmacol*, 2006, **46**(3): 337-344.
[59] Lv Xia, Xia YL, Finel M, *et al*. Recent progress and challenges in screening and characterization of UGT1A1 inhibitors [J]. *Acta Pharma Sin B*, 2019, **9**(2): 258-278.
[60] Lv X, Ge GB, Feng L, *et al*. An optimized ratiometric fluorescent probe for sensing human UDP-glucuronosyltransferase 1A1 and its biological applications [J]. *Biosens Bioelectron*, 2015, **72**: 261-267.
[61] Wang XX, Lv X, Li SY, *et al*. Identification and characterization of naturally occurring inhibitors against UDP-glucuronosyltransferase 1A1 in Psoraleae Fructus (Bu-gu-zhi) [J]. *Toxicol Appl Pharmacol*, 2015, **289**(1): 70-78.
[62] Levitt DG, Levitt MD. Quantitative assessment of the multiple processes responsible for bilirubin homeostasis in health and disease [J]. *Clin Exp Gastroenterol*, 2014, **7**: 307-328.
[63] 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 (Phila)*, 2009, **47**(7): 683-685.
[64] Li MY. Study on the main components of Psoralea inhibiting UDP-Glucuronosyltransferase (UGT) [D]. Jinzhou, Jinzhou Medical University, 2015.
[65] Zhang XS, Zhao ZQ, Qin ZS, *et al*. Herb-drug interaction between irinotecan and psoralidin-containing herbs [J]. *Eur J Drug Metab Pharmacokinet* , 2015, **40**(4): 481-484.
[66] Shan L, Yang S, Zhang G, *et al*. Comparison of the inhibitory potential of bavachalcone and corylin against UDP-Glucuronosyltransferases [J]. *Evid Based Complement Alternat Med* , 2014, **2014**, 4-16.
[67] Wang DD, Zou LW, Jin Q, *et al*. Human carboxylesterases: a comprehensive review [J]. *Acta Pharma Sin B*, 2018, **8**(05): 9-22.
[68] Sun DX, Ge GB, Dong PP, *et al*. Inhibition behavior of fructus psoraleae's ingredients towards human carboxylesterase 1 (hCES1) [J]. *Xenobiotica* , 2016, **46**(6): 503-510.
[69] Li YG, Hou J, Li SY, *et al*. Fructus Psoraleae contains natural compounds with potent inhibitory effects towards human carboxylesterase 2 [J]. *Fitoterapia*, 2015, 99-106.
[70] Song YQ, Guan XQ, Weng ZM, *et al*. Discovery of a highly specific and efficacious inhibitor of human carboxylesterase 2 by large-scale screening [J]. *Int J Biol Macromol*, 2019, **137**: 261-269
[71] Zou LW, Jin Q, Wang DD, *et al*. Carboxylesterase inhibitors: an update [J]. *Curr Med Chem*, 2018, **25**(14): 1627-1649.
[72] Han L, Wang YG, Ma ZC, *et al*. Inductive effects of psoralen, isopsoralen, bavachin and isobavachalcone cytochrome on P450 2B6 [J]. *Pharmacol Clin Chin Mater Med*, 2017, **33**(01), 15-19.
[73] Wang S, Dunlap TL, Howell CE, *et al*. Hop (*Humulus lupulus*) extractand 6-prenylnaringenin induce P450 1A1 catalyzed estrogen 2-hydroxylation [J]. *Chem Res Toxicol*, 2016, **29**(7): 1142-1150.
[74] Baumqart A, Schmidt M, Schmitz HJ, *et al*. Natural furocoumarins as inducers and inhibitors of cytochrome P450 1A1 in rat hepatocytes [J]. *Biochem Pharmacol*, 2005, **69**(4): 657-667.
[75] Lee, SJ, Nam KW, Mar W. Induction of quinone reductase activity by psoralidin isolated from *Psoralea corylifolia* in mouse hepa 1c1c7 cells [J]. *Arch Pharm Res*, 2009, **32**(7): 1061-1065.
[76] Lee SJ, Nam KW, Mar W. Effects of psoralen from *Psoralea corylifoliaon* quinone reductase, ornithine decarboxylase, and JB6 cells transformation promotion [J]. *Arch Pharm Res*, 2011, **34**(1): 31-36.
[77] Etta YL, Xu ML, Xia YJ, *et al*. Activation of G protein-coupled receptor 30 by flavonoids leads to expression of acetylcholinesterase in cultured PC12□cells [J]. *Chem Biol Interact*, 2019, **306**: 147-151.
[78] Dang Y, Ling S, Duan J, *et al*. Bavachalcone-induced manganese superoxide dismutase expression through the AMP- activated protein kinase pathway in human endothelial cells [J]. *Pharmacology*, 2015, **95**(3-4): 105-110.
[79] Graham DT. Regulation of proprietary traditional Chinese medicines in Australia [J]. *Chin J Nat Med*, 2017, **15**(1): 12-14.
[80] Li A, Gao M, Zhao N, *et al*. Acute liver failure associated with Fructus Psoraleae: a case report and literature review [J]. *BMC Complement Altern Med*, 2019, **19**(1): 84-87.
[81] Yu Y, Yu R, Men W, *et al*. Psoralen induces hepatic toxicity through PERK and ATF6 related ER stress pathways in HepG2 cells [J]. *Toxicol Mech Methods*, 2019, **8**: 1-9.
[82] Zhang RW. Traditional Chinese medicine: research and development, globalization, and regulation [J]. *Chin J Nat Med*, 2017, **15**(1): 1-3.
[83] Li K, Zhou N, Zheng XK, *et al*. Quantitative analysis, pharmacokinetics and metabolomics study for the comprehensive characterization of the salt-processing mechanism of Psoraleae Fructus [J]. *Sci Rep*, 2019, **9**(1): 661-670.

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