Department of Pharmacy[1], the Second Affiliated Hospital; College of Pharmacy[2], Harbin Medical University, Harbin, China

In vivo effects of scutellarin on the activities of CYP1A2, CYP2C11, CYP2D1, and CYP3A1/2 by cocktail probe drugs in rats

Zhiping Lin[1], Sixun Guo[1], Chunjuan Yang[2], Yue Yu[1], Lei Xu[1], Gaofeng Liu[1]

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Gaofeng Liu, Department of Pharmacy, the Second Affiliated Hospital of Harbin Medical University, Harbin, 150086, China
liugaofengwty@126.com

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Objective: To investigate the influence of scutellarin on the activities of CYP1A2, CYP2C11, CYP2D1, and CYP3A1/2 in rats *in vivo*. *Methods*: Scutellarin and saline were intravenously administered to male Wistar rats via the caudal vein for 7 days consecutively. On the 8th day, the rats were treated with probe drugs of caffeine (10 mg/kg), tolbutamide (10 mg/kg), metoprolol (20 mg/kg), dapsone (10 mg/kg) by intraperitoneal injection, and the blood samples were collected at different times. The probe drugs in the blood samples were measured by ultra performance liquid chromatography mass spectrometer (UPLC-MS/MS) and the changes of the pharmacokinetics parameters of the drugs were observed to evaluate the effects of scutellarin on the four CYP450 isoforms in rats. *Results:* The activity of CYP1A2 in rats was inhibited significantly after treatment with scutellarin by increased caffeine $t_{1/2}$ (21.76%, $P<0.05$), T_{max} (43.05%, $P<0.05$), C_{max} (43.92%, $P<0.01$) and $AUC_{0-\infty}$ (50.88%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control. The activity of CYP2C11 in rats was inhibited significantly after treatment with scutellarin by increased tolbutamide $t_{1/2}$ (16.74%, $P<0.01$), T_{max} (116.87%, $P<0.05$), C_{max} (63.78%, $P<0.01$) and $AUC_{0-\infty}$ (70.61%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control. The activity of CYP3A1/2 in rats was inhibited significantly after treatment with scutellarin by increased dapsone $t_{1/2}$ (45.28%, $P<0.05$), T_{max} (81.55%, $P<0.05$), C_{max} (155.58%, $P<0.01$) and $AUC_{0-\infty}$ (176.35%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control. The pharmacokinetic parameters of metoprolol were not significantly changed in the scutellarin-treated group compared with those of the blank control. *Conclusion:* Scutellarin could significantly inhibit CYP1A2, CYP2C11 and CYP3A1/2 activities in rats *in vivo,* but had no effects on the activity of CYP2D1.

1. Introduction

As the use of herbal products becomes more and more widespread, the potential herb-drug interactions have received great attention worldwide (Izzo and Ernst 2009; Chien et al. 2010). The interactions may lead to severe adverse drug reactions or decrease the therapeutic effects, which could significantly influence the rehabilitation of patients. Lots of metabolism-based drug interactions have been reported (Lan et al. 2008; Cheng et al. 2010). Cytochrome P450 s (CYP450) superfamily is the most important drug metabolizing enzyme system, and the major isoforms are CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (corresponding to CYP1A2, CYP2C11, CYP2D1, and CYP3A1/2 in rats), which are responsible for metabolizing more than 90% of drugs in the human body (Shimada et al. 1994). It is believed that inhibition and induction of CYP450 isozymes are the major causes for clinical herb-drug interactions (Kennedy and Seely 2010; Jaja et al. 2008).

Scutellarin (Fig. 1), is the main active ingredient of traditional Chinese medicinal herb *Erigeron breviscapus (Vant) Hand Mazz*. It has been investigated to have many pharmacological activities: antithrombolysis, anticoagulatory, antioxidative, anti-inflammatory, neuroprotective, vasorelaxation cardiovascular and cerebrovas-cular ischemia protective effects, etc. (Pan et al. 2008; Li et al. 2009; Tan et al. 2010; Zhang et al. 2009). Many preparations containing scutellarin as the main ingredient have been widely used in treatments of acute cerebral infarction,

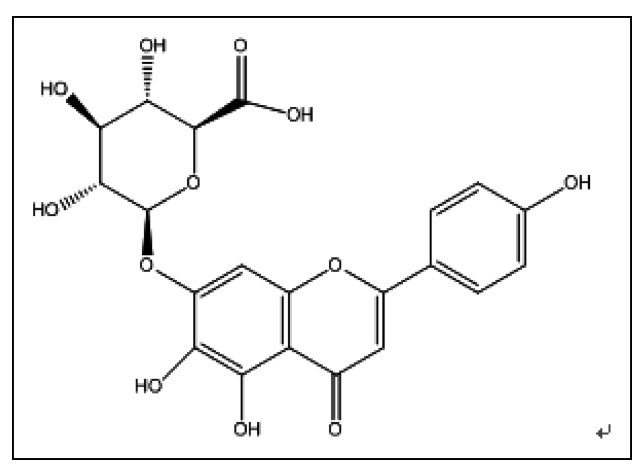

Fig. 1: Structure of scutellarin.

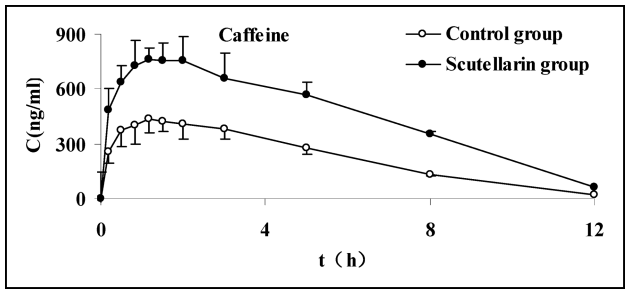

Fig. 2: Mean plasma concentration-time curve of caffeine after intraperitoneal administration of 10 mg/kg in rats with or without scutellarin treatment (10 mg/kg) for 7 days. Each value represents the mean ± s.d. of eight animals.

coronary disease, diabetes mellitus, nephropathy rheumatoid arthritis, chronic pulmonary heart disease, etc(Cao et al. 2008; Li et al. 2011), and they are often used in combination with western drugs, such as captopril, nimodipine, trimetazidine, etc. (Zhong et al. 2008; Peng 2004; Wu 2013). Despite the broad therapeutic uses of scutellarin, however, there have been no reports for its effects on the activities of the four CYP450 isoforms. It remains unknown whether scutellarin co-administering with other drugs would result in CYP450-mediated herb-drug interactions. The goal of this work is to investigate the influence of scutellarin on the activities of the four CYP450 isoforms in rats *in vivo* and predict the potential metabolism-based drug interactions arising from scutellarin.

2. Investigations and results

2.1. Concentration-time curves and pharmacokinetic parameters of the four probe drugs

UPLC-MS-MS was used to determine the concentrations of caffeine, tolbutamide, metoprolol, and dapsone in blood samples (Liu et al. 2013). The concentration-time curves are shown in Figs. 2–5. The pharmacokinetic parameters are shown in Table 1. The statistical results of pharmacokinetics parameters of the scutellarin-treated group compared with those of the blank control are shown in Table 2.

2.2. Effects of scutellarin on CYP1A2

As shown in Table 1 and Fig. 2, scutellarin slowed down the metabolism of caffeine, suggesting that the activity of CYP1A2 in rats was significantly inhibited after treatment with scutellarin which increased caffeine $t_{1/2}$ (21.76%, $P<0.05$), T_{max} (43.05%, $P<0.05$), C_{max} (43.92%, $P<0.01$) and $AUC_{0\text{-}\infty}$ (50.88%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control.

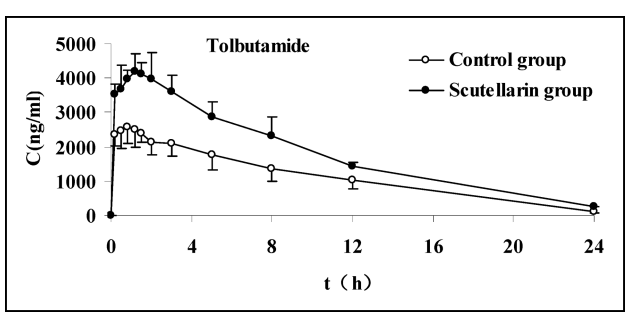

Fig. 3: Mean plasma concentration-time curve of tolbutamide after intraperitoneal administration of 10 mg/kg in rats with or without scutellarin treatment (10 mg/kg) for 7 days. Each value represents the mean ± s.d. of eight animals.

Table 1: Pharmacokinetics parameters of the four probe drugs ($\bar{X} \pm s$, n = 8)

	Caffeine		Tolbutamide		Metoprolol		Dapsone	
	Control group	Scutellarin group	Control group	Scutellarin group	Control group	Scutellarin group	Control group	Scutellarin group
$t_{1/2}$/h	2.05 ± 0.11	2.62 ± 0.44*	4.48 ± 0.39	5.23 ± 0.34**	2.15 ± 1.62	1.89 ± 0.39	7.42 ± 1.88	10.78 ± 3.89*
T_{max}/h	1.27 ± 0.50	2.23 ± 0.78*	0.83 ± 0.41	1.80 ± 0.85*	0.30 ± 0.30	0.30 ± 0.30	1.03 ± 0.56	1.87 ± 0.76*
C_{max}/ng·ml^{-1}	467.06 ± 73.88	832.86 ± 118.65**	1856.47 ± 223.32	3040.45 ± 244.62**	60.09 ± 11.27	63.44 ± 7.90	111.61 ± 22.96	285.25 ± 48.15**
$AUC_{0\text{-}t}$/ng·h·ml^{-1}	2705.76 ± 373.05	5461.88 ± 583.98**	18201.43 ± 3409.15	28791.11 ± 2921.20**	136.36 ± 73.93	133.29 ± 28.64	703.19 ± 429.40	1808.01 ± 243.21**
$AUC_{0\text{-}\infty}$/ng·h·ml^{-1}	2795.67 ± 368.99	5691.37 ± 652.27**	20913.60 ± 3584.12	35680.71 ± 5729.09**	175.34 ± 92.33	150.49 ± 37.14	875.02 ± 582.37	2418.16 ± 367.68**
CL(L·h^{-1})	0.0007 ± 0.00012	0.0004 ± 0.00003*	20.00017 ± 0.00004	0.00011 ± 0.00001**	0.0445 ± 0.0406	0.03125 ± 0.0073	0.0038 ± 0.0021	0.00112 ± 0.0002*

* $P<0.05$, ** $P<0.01$, compared with those of the control

Table 2: *P* Values of the pharmacokinetics parameters of the four probe drugs

	Caffeine	Tolbutamide	Metoprolol	Dapsone
$t_{1/2}$/h	0.02011*	0.00596**	0.37324	0.04942*
T_{max}/h	0.02615*	0.03136*	0.50000	0.04281*
C_{max}/ng·ml^{-1}	0.00037**	0.00002**	0.30096	0.00021**
AUC_{0-24}/ng·h·ml^{-1}	0.000027**	0.00041**	0.46712	0.00105**
$AUC_{0-\infty}$/ng·h·ml^{-1}	0.000046**	0.00100**	0.29914	0.00086**

* $P<0.05$, ** $P<0.01$, compared with those of the blank control.

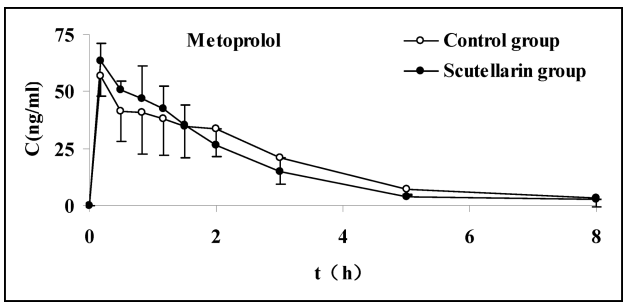

Fig. 4: Mean plasma concentration-time curve of metoprolol after intraperitoneal administration of 20 mg/kg in rats with or without scutellarin treatment (10 mg/kg) for 7 days. Each value represents the mean ± s.d. of eight animals.

2.3. Effects of scutellarin on CYP2C11

The blood concentration-time curves and pharmacokinetics parameters of tolbutamide are shown in Table 1 and Fig. 3. Scutellarin significantly inhibited the activities of CYP2C11, and increased tolbutamide $t_{1/2}$ (16.74%, $P<0.01$), T_{max} (116.87%, $P<0.05$), C_{max} (63.78%, $P<0.01$), and $AUC_{0-\infty}$ (70.61%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control.

2.4. Effects of scutellarin on CYP2D1

The blood concentration-time curves and pharmacokinetics parameters of metoprolol are shown in Table 1 and Fig. 4. The pharmacokinetic parameters of metoprolol were not significantly changed in the scutellarin-treated group compared with those of the blank control group, which indicated that scutellarin had no effects on the activity of CYP2D1.

2.5. Effects of scutellarin on CYP3A1/2

The blood concentration-time curves and pharmacokinetics parameters of metoprolol are shown in Table 1 and Fig. 5. Scutellarin significantly inhibited the activities of CYP3A1/2 in rats

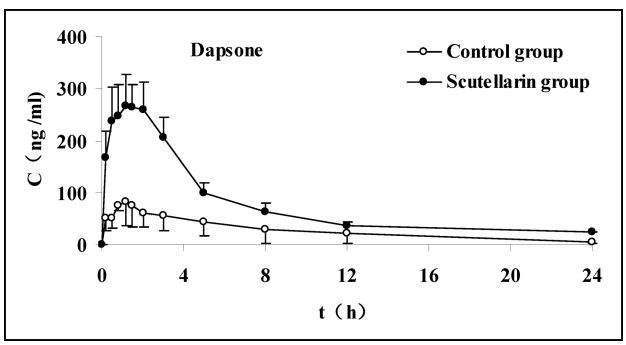

Fig. 5: Mean plasma concentration-time curve of dapsone after intraperitoneal administration of 10 mg/kg in rats with or without scutellarin treatment (10 mg/kg) for 7 days. Each value represents the mean ± s.d. of eight animals.

and increased dapsone $t_{1/2}$ (45.28%, $P<0.05$), T_{max} (81.55%, $P<0.05$), C_{max} (155.58%, $P<0.01$), and $AUC_{0-\infty}$ (176.35%, $P<0.01$) in the scutellarin-treated group compared with those of the blank control.

3. Discussion

In this study, caffeine, tolbutamide, metoprolol, and dapsone were chosen as the probe drugs of CYP1A2, CYP2C11, CYP2D1, and CYP3A1/2, respectively. The effects of scutellarin on the four CYP450 isoforms in rats were studied by comparing the pharmacokinetic parameters of the four probe drugs between the scutellarin-treated and the blank control groups.

According to the results, scutellarin slowed down the metabolism of caffeine in the scutellarin-treated group, which indicated that the activity of CYP1A2 in rats was significantly inhibited after treatment with scutellarin. Human CYP1A2 is homolog to rat CYP1A2. Clinically, many drugs such as theophylline, propranolol, propafenone, verapamil, amitriptyline, clozapine, acarbazine, paracetamol, lidocaine, and nifedipine, are metabolized by CYP1A2 (China National Formulary 2010; Nian et al. 2010), so when they are co-administered with scutellarin, great attention should be paid to the possible herb-drug interations, especially for the drugs with narrow therapeutic windows such as theophylline.

Scutellarin restrained the metabolism of tolbutamide in the scutellarin-treated group, which showed that scutellarin inhibited the activities of CYP2C11 *in vivo* in rats. In theory, human CYP2C9 is homolog to rat CYP2C11. When scutellarin is administered with CYP2C9 substrates like celecoxib, diclofenac, ibuprofen, indomethacin, glipizide, glyburide, tolbutamide, fluvastatin, irbesartan, phenytoin, S-warfarin, and sulfisoxazole (China National Formulary 2010; Nian et al. 2010), the metabolism of the drugs may be restrained, and the adverse drug reactions may be increased. Among those drugs, warfarin is currently the most widely used anticoagulant, which with narrow therapeutic windows, so special attention should be given. The metabolism of warfarin would be slowed down resulting from the inhibition of CYP2C9, which would increase the plasma concentration of warfarin, and the risk of bleeding would increase.

Scutellarin slowed down the metabolism of dapsone in the scutellarin-treated group, which meant that scutellarin inhibited the activities of CYP3A1/2 *in vivo* in rats. Human CYP3A4 is considered to be homolog to rat CYP3A1/2. When scutellarin is administered together with CYP3A4 substrates like amitriptyline, carbamazepine, clozapine, diazepam, estazolam, cocaine, fentanyl, ketamine, methadone, erythromycin, itraconazole, cyclosporin A, clarithromycin, ethosuximide, nifedipine, nateglinide, omeprazole, pioglitazone, quinidine, atorvastatin, simvastatin, testosterone, dapsone, verapamil, lidocaine, diltiazem, digoxin, and chlorpheniramine (China National Formulary 2010; Nian et al. 2010), the metabolism of the drugs may be restrained, and the incidence of adverse drug reactions may be increased. Particularly, digoxin, with narrow therapeutic index, is widely used in the treatment of heart failure, so is worthy of our concern.

No significant differences of the pharmacokinetics parameters of metoprolol were observed between the scutellarin-treated group and the control group in this study, which indicated that the activity of CYP2D1 was not affected by scutellarin. Human CYP2D6 is generally thought to be homolog to rat CYP2D1. Tramadol, codeine, imipramine, debrisoquine, amphetamine, chlorpromazine, perphenazine, chlorpheniramine, metoprolol, putealol, doxorubicin, metoclopramide, mexiletine, propafenone, dex-

tromethorphan are substrates of CYP2D6 (China National Formulary 2010; Nian et al. 2010). It could be speculated that if scutellarin is co-administered with the substrates of CYP2D6, the metabolic herb-drug interactions may not occurred.

Clinically, scutellarin preparations were widely used for treatment of cerebrovascular diseases. It was reported that Breviscapine tablet (containing scutellarin 20 mg per tablet) had great effects in the treatment of senile dementia, senile dyslipidemia, and acute facial nerve inflammation (Liu et al. 1997; Dai 2004; Zeng 2009). Breviscapine injection (5 mL containing scutellarin 10 mg) had definite curative effects on treating hypertension nephropathy (Ye 2013). Dengzhan Shengmai capsule (containing scutellarin 15 mg per capsule) had good clinical effects on cerebral infarction (Lin et al.2013). Dengzhanxixin injection (containing scutellarin 0.40 ∼ 0.60 mg per ampoule) had definite curative effects in the amelioration of symptoms and ECG improvement in the treatment of coronary heart disease angina pectoris (Xiang et al. 2012). It's also very popular that scutellarin preparations are co-administered with other drugs in clinic. Studies showed that Dengzhanxixin injection, when co-administering with aspirin, nitrates, β-blockers, statins, edaravone, and ozagrel, had good clinical effects on unstable angina, acute ischemic stroke, acute cerebral infarction (Nie et al. 2012; Shen 2012; Niu 2013). Breviscapine injection co-administering with enteric-coated aspirin, citicoline, vitamins, simvastatin, and clopidogrel sulfate had remarkable curative effects in the treatment of acute cerebral infarction (Wang 2013; Zhang 2013; Cui 2013). It was of great advantage to the treatment of pulmonary heart failure when breviscapine injection combined with phentolamine (Du et al. 2002). However, there were also reports that adverse drug reactions in the application of these preparations were partly caused by drug combination (Xie and Ma 2009), and the real reasons are not clear up to now. All these preparations contain scutellarin as the main active ingredient, so the finding of this paper is of great importance for predicting herb-drug interactions and possible adverse drug reactions.

In conclusion, the present study demonstrated that scutellarin inhibited the activities of CYP1A2, CYP2C11 and CYP3A1/2, and had no effects on the activity of CYP2D1 in rats *in vivo*. Our result about CYP1A2 is in good agreement with the previous report, which indicated that scutellarin might have an inhibitory effect on rat CYP1A2 *in vitro* and *in vivo* (Jian et al. 2012). The results about CYP2C11, CYP3A1/2 and CYP2D1 are firstly reported in our present study. The findings of the study are of importance in predicting the potential herb-drug interactions, which is important for safe and effective drug use. However, it was suggested that there are species differences for metabolism of drugs, so the clinical meanings of effects of scutellarin on CYP450 s need to be investigated further.

4. Experimental

4.1. Chemicals and materials

Scutellarin (98%) was purchased from Chengdu Mansite Pharmaceutical Company (Chengdu, China). Caffeine, metoprolol, and phenacetin were obtained from the National Institute for the Control of Pharmaceutical and Biological Products. Tolbutamide was obtained from Dr. Ehrenstorfer (Augsburg, Germany). Dapsone was supplied by Sigma Chemical Co. (St Louis, MO, USA). Methanol and formic acid were of HPLC grade, and acetonitrile was of hypergrade for LC-MS. All other reagents were of analytical grade. The mixture solutiton of the probe drugs were dissolved with normal saline including proper polysorbate 80.

4.2. Sample preparation

Twenty microliters phenacetin (IS) solution (10 μg/mL) was added to 100 μL rat plasma samples. Then the samples were extracted with 2.0 mL dichloromethane-butanol (10:1, v/v). After vortexing for 3 min and centrifugation at 5,000 × g for 5 min, the organic phase was transferred to another tube and evaporated to dryness in a 40 °C water bath under a gentle stream of nitrogen. The residue was reconstituted with 200 μL mobile phase. Finally, an aliquot of 10 μL was injected into the UPLC–MS-MS system for analysis.

4.3. Instrumentation and UPLC–MS-MS determining conditions

Chromatographic analyses were performed with an Acquity UPLC system (Waters, Milford, MS, USA) and separations were achieved using an Acquity UPLC BEH HILIC column (2.1 × 50 mm, 1.7 μm) from Waters. The column temperature was maintained at 40 °C. The sampler chamber temperature in the autosampler was kept at 10 °C. The mobile phase consisted of acetonitrile and water (containing 0.1% formic acid) at a flow rate of 0.25 mL/min, and the total run time of each injection was 5 min.

MS-MS detection was performed on a Waters Micromass Quattro Micro API triple quadrupole tandem MS (Waters, Manchester, UK). The instrument was operated using an electrospray (ESI) source in positive mode. The ionisation source parameters were: capillary voltage 3.3 KV, cone voltage 30 V, source temperature 120 °C, and desolvation gas (nitrogen) heated at 350 °C (650 L/h). Cone gas flow rate was 50 L/h. Quantification was performed in selected ion recording (SIR) mode at m/z 195.23 for caffeine, 271.28 for tolbutamide, 268.31 for metoprolol, 249.25 for dapsone, and 180.21 for phenacetin, respectively. Instrument control and data acquisition were performed using MassLynx^{TM} V 4.1 software.

4.4. Animals and treatment

Wistar rats (200 ± 20 g, male) were supplied by the Animal Experimental Center of Harbin Medical University, which was fully accredited by the Institutional Animal Care and Use Committee (IACUC). All rats were handled in a manner that met all the recommendations formulated by the National Society for Medical Research and Guidelines for the Care and Use of Laboratory Animals.

The rats were randomly divided into blank control and scutellarin-treated groups, eight rats in each group. These two groups were administered 0.2 mL physiological saline and scutellarin (10 mg/kg) by caudal vein for seven consecutive days, respectively; the next day, they were given probe drugs of caffeine (10 mg/kg), tolbutamide (10 mg/kg), metoprolol (20 mg/kg) and dapsone (10 mg/kg) by intraperitoneal injection. All the rats were fasted overnight before the experiments. Blood samples were collected from the caudal vein at 0 (pre-dose), 0.17, 0.5, 0.83, 1.17, 1.5, 2, 3, 5, 8, 12 and 24 h and were put into heparinized test tubes. The samples were centrifuged at 5,000 × g for 10 min to separate the plasma and were stored at −20 °C until used.

4.5. Statistical analysis

Data were expressed as means ± standard deviation (*S.D.*) and analyzed by the Dunnett's test. Pharmacokinetic parameters were derived with a nonlinear regression iterative program; the calculations were carried out using the DAS 2.0 pharmacokinetics program (Chinese Pharmacological Society). $P < 0.05$ and $P < 0.01$ were considered to be statistically significant and highly significant, respectively.

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