

## • Research Papers •

## Pharmacokinetic Study of Baicalein and Its Major Metabolites after iv Administration in Dogs

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**Abstract:** **Objective** To develop and validate a simple, rapid, sensitive, and reproducible HPLC method for simultaneous determination of baicalein and its metabolite baicalin in dog plasma and for the subsequent pharmacokinetic study after iv administration to dogs. **Methods** An accurate and reproducible HPLC-UV method was developed and validated for simultaneous determination of baicalein and baicalin in dog plasma, using luteolin as internal standard. The analytes were separated by an Agilent Zorbax SB-C<sub>18</sub> column (250 mm × 4.6 mm, 5 μm) and the column temperature was maintained at 40 °C. The mobile phase was a binary mixture of acetonitrile and water (27:73), containing 0.05% phosphoric acid in water, with a flow rate of 1.0 mL/min. The UV detector was set at 276 nm. **Results** Linear relationships were validated over the range of 0.05–25 μg/mL for baicalein and 0.05–20 μg/mL for baicalin. The intra- and inter-day precision values for all samples were within 8.0%, using relative standard deviation. This method was successfully applied to the pharmacokinetic studies in dogs after iv administration of baicalein. Baicalein was converted to baicalin quickly. *C*<sub>max</sub> values were 21.13 μg/mL at 0.05 h for baicalein and 1.57 μg/mL at 0.5 h for baicalin, areas under the plasma concentration-time curve were 4.97 h·μg/mL for baicalein and 0.63 h·μg/mL for baicalin, and the elimination half-life is 0.50 h for baicalein and 0.75 h for baicalin, respectively. **Conclusion** The method is able and sufficient to be used in drug metabolism and pharmacokinetic studies of baicalein.

**Key words:** baicalein; baicalin; HPLC; pharmacokinetics; plasma

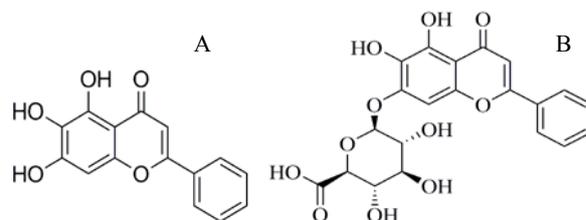
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### Introduction

Baicalein and baicalin, a flavone aglycone and its glucuronide (Fig. 1), are flavonoids from the roots of *Scutellaria baicalensis* Georgi., which is widely used in traditional Chinese medicine (You *et al.*, 2010). It is well known that baicalein and baicalin exhibit a broad of pharmacological activities, such as anti-oxidative (Shieh, Liu, and Lin, 2000), antiviral (Hu *et al.*, 2010), anticancer (Gao *et al.*, 2010; Zhou *et al.*, 2009), and antipruritic (Trinh *et al.*, 2010) effects. Neuroprotective effects of baicalein and baicalin have also been reported

in *in vivo* and *in vitro* studies in recent years (Mu *et al.*, 2009; Cheng *et al.*, 2008; Jiang *et al.*, 2010; Zhu *et al.*, 2007).

Some researchers have focused on pharmacokinetic studies of baicalein in rats (Zhang, Lin, and



**Fig. 1** Chemical structures of baicalein (A) and baicalin (B)

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Zuo, 2004; Kotani *et al*, 2006; Gong *et al*, 2009; Deng, Yang, and Mou, 2008). Previous studies in rats showed that baicalein was obviously converted to baicalin during first pass after ig administration (Zhang *et al*, 2005). It was reported that baicalein was also partly transformed into baicalin after iv administration in rats. Zhang *et al* (2005) reported that baicalein was quickly metabolized to baicalin and achieved peak area within 10 min after iv administration of 10 mg/kg of baicalein in rats. According to their study, baicalein could not be detected after 20 min of the dosing, whereas baicalin could still be detected 6 h after dosing. Another experiment (Zhang, Lin, and Zuo, 2004) was performed with a dose of 37  $\mu\text{mol/kg}$  iv administrated to rats and got the similar results. Neither baicalein nor baicalin can be detected after 8 h in rats.

In order to investigate the pharmacokinetic profiles during preclinical studies, it is essential to carry out experiments in different animals. Up to now, few studies regarding the pharmacokinetic profiles of baicalein have been described in animals rather than rats. The aim of this study was developing and validating a simple, rapid, sensitive, and reproducible HPLC method for simultaneous determination of baicalein and baicalin in dog plasma and for the subsequent pharmacokinetic study after iv administration to dogs.

## Materials and methods

### Chemicals and reagents

All organic solvents were of HPLC-grade purity and were purchased from Honeywell (USA). Baicalein (purity > 99%) was provided by Prof. LU Yang (Institute of Materia Medica, Chinese Academy of Medical Sciences). Baicalin (purity > 98%) was purchased from Mansite Pharmaceutical Co., Ltd. (Chengdu, China). Luteolin (IS, purity > 98%) was purchased from Shanxi Huike Botanical Development Co., Ltd. (Shanxi, China). Other chemicals were all of analytical grade.

### Establishment of bioanalytical method

**Instrument and analytical conditions** Liquid chromatography was performed using an Agilent HPLC 1100 system, equipped with a binary pump, an online vacuum degasser, an auto-sampler, a thermo stated column compartment, a diode array detector, and the ChemStation software.

The separation of samples was carried out on an Agilent Zorbax SB-18 column (250 mm  $\times$  4.6 mm, 5  $\mu\text{m}$ ). The mobile phase was a mixture of acetonitrile and water (27:73), containing 0.05% phosphoric acid in water. The flow rate was set at 1.0 mL/min. The injection volume was 40  $\mu\text{L}$  and the column temperature was maintained at 40  $^{\circ}\text{C}$ . The wavelength of UV detector was set at 276 nm.

**Preparation of stock solutions** The stock solutions of baicalein and baicalin were prepared in methanol at 1.0 mg/mL, respectively. IS solution was prepared at 0.1 mg/mL using methanol for dilution. The stock solution and IS solution were stored at  $-20^{\circ}\text{C}$  until used. Working solutions of baicalein and baicalin were prepared in methanol by appropriate dilution of the stock solution.

**Preparation and quality control of samples** Thawed plasma sample (100  $\mu\text{L}$ ) was mixed with 5  $\mu\text{L}$  vitamin C (10 mg/mL) to keep samples stable and 5  $\mu\text{L}$  IS solution was added. The mixture was used for precipitation with addition of 30  $\mu\text{L}$  acetonitrile-perchloric acid (4:1). The samples were vortex-mixed for 1 min and then centrifuged at 13 400 r/min for 10 min at 4  $^{\circ}\text{C}$ . The upper phase was transferred to an auto-sampler vial and 40  $\mu\text{L}$  was injected into the column for analysis.

Quality control (QC) samples were prepared by spiking blank Beagle's dog plasma with proper volume of the reference solution to produce a required concentration of baicalein and baicalin (0.1, 1.0, and 10.0  $\mu\text{g/mL}$ ), respectively. The following procedures were the same as described above. The QC samples for the determination of precision, accuracy, and stability were prepared and stored at  $-20^{\circ}\text{C}$  until used.

### Selectivity

Selectivity of the present method was ascertained by analyzing six blank dog plasma samples, prepared according to the proposed extraction procedure and chromatographic conditions, to exclude the interference by the analytes and IS.

### Calibration curves and lower limit of detection

Calibration curves were prepared by spiking blank Beagle's dog plasma with proper volume of working solutions to produce the calibration curve points ranging from 0.05 to 25.0  $\mu\text{g/mL}$  for baicalein and ranging from 0.05 to 20.0  $\mu\text{g/mL}$  for baicalin. Blank

plasma samples were analyzed to confirm the absence of interference, but not used for calibration. The lower limit of quantification (LLOQ) was determined as the concentrations with a signal-to-noise ratio of 10.

#### **Precision and accuracy**

The precision of the assay was determined from the QC samples by replicating analytes of three concentration levels as described above. Intra-day precision and accuracy were evaluated by analyses of QC samples on one day ( $n = 5$ ). Inter-day precision and accuracy were determined by repeated analyses of QC samples over consecutive five days.

#### **Extraction recovery**

The extraction recoveries of baicalein and baicalin were determined at low, medium, and high concentrations, respectively. Recoveries were calculated by comparing the analytes-IS peak area ratios obtained from extracted plasma samples with those from reference solutions at the same concentration.

#### **Stability**

The stability of baicalein and baicalin was evaluated at three concentration levels in five replicates under conditions mimicking situations likely to be encountered during sample storage, post-preparation, and the analytical process, including  $-80\text{ }^{\circ}\text{C}$  storage in stock solution for three weeks, room temperature storage in rat plasma for 4 h, three freeze-thaw cycles, and auto-sampler storage in the reconstitution solution for 24 h. Samples were considered to be stable if assay values were within the acceptable limits of accuracy and precision ( $\pm 15\%$  of RSD).

#### **Pharmacokinetic study**

Three male and three female Beagle's dogs with body weight of 7.0–8.1 kg were purchased from Nanjing Yadong Laboratory Animals Research Center (Nanjing, China). The dogs were housed individually in cages. They had free access to water and were fed daily with a laboratory canine diet. The dogs were maintained in air-conditioned animal quarters with alternating 12 h light/dark cycles at room temperature of  $(22 \pm 2)\text{ }^{\circ}\text{C}$  and with relative humidity of  $(50 \pm 10)\%$ . The dogs were acclimated to the facilities for 15 d before experiments. This experiment was conducted in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care International and the animals were maintained in

accordance with the *Guide for the Care and Use of Laboratory Animals*. The animals were fasted for 12 h and had free access to water throughout the experimental period.

About 2 mL of venous blood sample was collected into heparinized tubes pre-dose and at 0.03, 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.5, and 2 h after iv administration of a single dose of baicalein at 10.0 mg/kg. The blood samples were centrifuged at 4500 r/min for 10 min at  $4\text{ }^{\circ}\text{C}$  and the plasma samples were stored at  $-80\text{ }^{\circ}\text{C}$  until analysis.

#### **Data analysis**

The plasma concentration-time data and relative parameters for baicalein and baicalin in dogs were obtained from Kinetic 4.4.1 software (Thermo Scientific, USA), employing a non-compartmental model.

## **Results and discussion**

### **Optimization of chromatographic conditions and sample preparation**

IS is required to keep accuracy when liquid-liquid extraction method is used. Luteolin was chosen as IS due to its structure similarity to the target compounds, retention action, and extraction efficiency.

Liquid-liquid extraction was used for samples purified. Methanol, ethyl acetate, and acetonitrile-perchloric acid (4:1) mixture were all tested. Finally, acetonitrile-perchloric acid (4:1) mixture was chosen for its high purification and extraction efficiency.

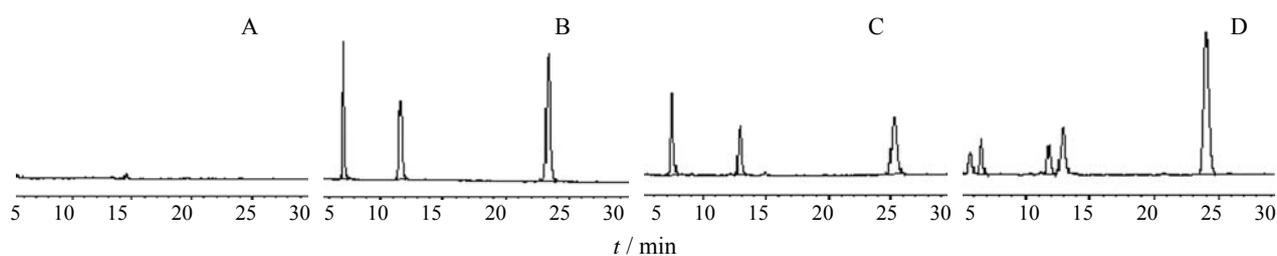
During samples preparation, vitamin C was used as an anti-oxidant to prevent drug degradation.

#### **Selectivity**

Chromatograms for baicalein, baicalin, and IS in actual plasma samples are presented in Fig. 2. Baicalein, baicalin, and IS were completely separated and there were no endogenous compounds or other impurities interfering with the assay. The retention times of baicalein, baicalin, and IS were approximately 23.4, 7.1, and 11.6 min, respectively. In addition, compared with other three figures, Fig. 2D showed another two peaks at the retention times of 6.4 and 13.5 min. It demonstrated that baicalein could convert to several other metabolites.

#### **Calibration curves and LLOQ**

The calibration curves were constructed with a peak area ratio of baicalein or baicalin to IS versus



**Fig. 2 HPLC chromatograms of baicalein (23.4 min), baicalin (7.1 min), and IS (11.6 min)**

A: blank plasma B: reference solution of baicalein, baicalin, and IS C: blank dog plasma with baicalein, baicalin, and IS D: dog plasma sample after iv administration of baicalein

plasma concentration ranging from 0.05 to 25  $\mu\text{g/mL}$  for baicalein and 0.05 to 20  $\mu\text{g/mL}$  for baicalin. The mean regression equations from five replicate calibration curves were listed in Table 1. The LLOQ for baicalein and baicalin were proved to be 0.05  $\mu\text{g/mL}$ .

#### Precision and accuracy

Data for intra- and inter-day precision and accuracy of the method for baicalein and baicalin are presented in Table 2. The precision and accuracy were

**Table 1 Linear regression data of baicalein and baicalin**

Compounds	Regression equations	$r^2$
baicalein	$R = 0.3840C + 0.0014$	0.9998
baicalin	$R = 0.2875C + 0.0005$	0.9999

**Table 2 Precision and recovery of baicalein and baicalin ( $\bar{x} \pm s, n = 5$ )**

Analyte	NC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	Intra-day assay		Inter-day assay		Recovery	
		MC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	RSD / %	MC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	RSD / %	Mean / %	RSD / %
Baicalein	0.1	$0.11 \pm 0.00$	2.96	$0.11 \pm 0.00$	2.47	104.34	7.45
	1	$0.97 \pm 0.04$	3.96	$0.97 \pm 0.01$	1.45	101.73	1.52
	10	$10.07 \pm 0.07$	0.72	$9.74 \pm 0.28$	2.84	98.48	3.05
Baicalin	0.1	$0.12 \pm 0.00$	2.78	$0.12 \pm 0.00$	1.44	116.24	2.04
	1	$1.03 \pm 0.03$	3.28	$1.04 \pm 0.06$	5.81	106.64	2.31
	10	$9.65 \pm 0.14$	1.41	$9.47 \pm 0.76$	8.04	96.24	1.92

#### Stability

The stabilities of baicalein and baicalin were evaluated under conditions during sample storage and processing, including freeze-thaw cycles, short-term, long-term, and post-preparative storage. As summarized in Table 3, the RSD values were all less than 11.5%. These findings indicated that the analytes were acceptably stable under the tested conditions.

According to these results, we could conclude that the developed and validated method was sensitive and reliable, which met the requirements of pharmacokinetic study (Liu, Wei, and Li, 2001; Xia, 2001; Wei *et al.*, 2010).

assessed by calculating the RSD for QC samples. The precision and accuracy for both intra- and inter-day were all within 9% at any concentration level, indicating good precision, accuracy, and reproducibility.

#### Recovery

The recoveries of baicalein and baicalin were evaluated using QC samples and calculated by comparing the peak area of extracted plasma sample with that of unextracted reference solution of the same concentration. The recoveries were from 98.48% to 104.34% for baicalein and 96.24% to 116.24% for baicalin (Table 2), which met the requirements of quantification experiment (NC: nominal concentration; MC: measured concentration).

#### Pharmacokinetic study

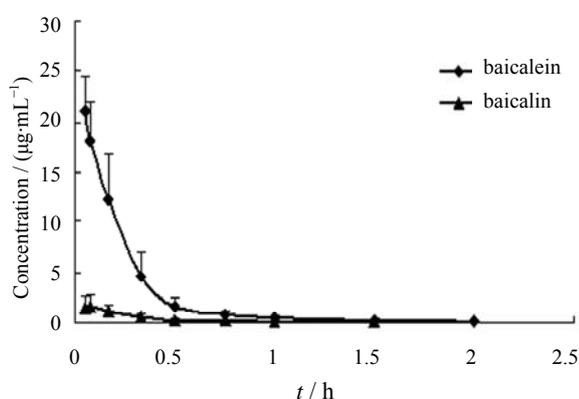
Pharmacokinetic study was carried out by the described method after iv administration of baicalein at 10.0 mg/kg in dogs. The mean plasma concentration-time curves of baicalein and its metabolite baicalin are shown in Fig. 3. The results revealed that baicalein was immediately converted to baicalin after administration and baicalin reached the peak concentration quickly.

The pharmacokinetic parameters are listed in Table 4.

The mean peak concentration ( $C_{\text{max}}$ ) was achieved at 0.05 h in 21.13  $\mu\text{g/mL}$  for baicalein and at 0.08 h in 1.57  $\mu\text{g/mL}$  for baicalin. The mean area under the plasma concentration-time curve (AUC) of baicalein

**Table 3** Stability of baicalein and baicalin in dog plasma ( $\bar{x} \pm s, n = 5$ )

Groups	Baicalein			Baicalin		
	NC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	MC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	RSD / %	NC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	MC / ( $\mu\text{g}\cdot\text{mL}^{-1}$ )	RSD / %
Freeze-thaw	0.1	0.107 $\pm$ 0.012	11.415	0.1	0.110 $\pm$ 0.006	5.229
	1.0	0.997 $\pm$ 0.039	3.905	1.0	1.033 $\pm$ 0.036	3.487
	10.0	10.147 $\pm$ 0.266	2.621	10.0	9.018 $\pm$ 0.095	1.058
Short-term	0.1	0.111 $\pm$ 0.004	3.836	0.1	0.116 $\pm$ 0.003	2.396
	1.0	0.955 $\pm$ 0.022	2.319	1.0	0.997 $\pm$ 0.034	3.382
	10.0	9.748 $\pm$ 0.087	0.891	10.0	9.130 $\pm$ 0.219	2.398
Long-term	0.1	0.109 $\pm$ 0.009	7.915	0.1	0.114 $\pm$ 0.002	2.180
	1.0	0.967 $\pm$ 0.012	1.263	1.0	0.988 $\pm$ 0.030	3.017
	10.0	9.992 $\pm$ 0.104	1.037	10.0	9.206 $\pm$ 0.172	1.868
Post-preparative	0.1	0.104 $\pm$ 0.003	2.749	0.1	0.105 $\pm$ 0.011	10.741
	1.0	1.017 $\pm$ 0.010	1.028	1.0	1.032 $\pm$ 0.094	9.136
	10.0	10.007 $\pm$ 0.390	3.892	10.0	9.499 $\pm$ 0.296	3.114

**Fig. 3** Mean plasma concentration-time of baicalein and baicalin in dogs after iv administration of 10.0 mg/kg baicalein ( $\bar{x} \pm s, n = 6$ )**Table 4** Pharmacokinetic parameters of baicalein and baicalin after iv administration of 10.0 mg/kg baicalein

Parameters	Unit	Baicalein	Baicalin
$C_{\max}$	$\mu\text{g}\cdot\text{mL}^{-1}$	21.13	1.57
$t_{\max}$	h	0.05	0.08
AUC	$\text{h}\cdot\mu\text{g}\cdot\text{mL}^{-1}$	4.97	0.63
$t_{1/2}$	h	0.50	0.75
MRT	h	0.34	0.76
CL	$\text{L}\cdot\text{h}\cdot\text{kg}^{-1}$	1.73	13.04
Vd	$\text{L}\cdot\text{kg}^{-1}$	1.24	14.36

was 4.97  $\text{h}\cdot\mu\text{g}/\text{mL}$  and that of baicalin was 0.63  $\text{h}\cdot\mu\text{g}/\text{mL}$ . The elimination half-life ( $t_{1/2}$ ) was 0.50 h for baicalein and 0.75 h for baicalin. The levels of baicalein and baicalin in plasma declined to less than 0.05  $\mu\text{g}/\text{mL}$  after 2 and 1.5 h, respectively.

In contrast with previous studies in rats (Zhang, Lin, and Zuo, 2004; Lai *et al.*, 2003), the results obtained from dogs showed that the  $C_{\max}$  was much higher and only a small part of baicalein converted into

baicalin after iv administration of baicalein. Also, both baicalein and baicalin were eliminated quickly. Comparison of each part in Fig. 2, additional peaks were shown in Fig. 2D, which indicated that baicalein might be converted to other metabolites and baicalin may not be the major metabolite of baicalein in dogs.

According to the results described above, we can conclude that the pharmacokinetic process of baicalein *in vivo* may be different among species due to different levels of metabolic enzymes. Further metabolic studies in dogs should be performed to reconfirm the conclusions in the future.

## Conclusion

An HPLC-UV method for simultaneous determination of baicalein and its major metabolite baicalin with luteolin as IS in Beagle's dog plasma has been developed and validated with satisfactory linear relationship, accuracy, stability, and adequate reproducibility. The analytical method could be further applied to the pharmacokinetics study of baicalein after a single dose iv administration in Beagle's dogs successfully for the first time, which indicates that our method is able and sufficient to be used in drug metabolism and pharmacokinetic studies of baicalein.

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## Captions of Cover Photo



*Convallaria majalis* L., also named lily of the valley, is the unique species in *Convallaria* L. It is a common used herb medicine mainly distributed in Europe, North America, Korea, Japan, and China. The main constituents include convallatoxin, convallarin, convallamarin, *etc.* *C. majalis* can strengthen heart and promote diuresis, and is clinically used to treat congestive heart failure, atrial fibrillation, and left heart failure caused by high blood pressure and nephritis.

Provided by ZHOU You  
Tonghua Normal University