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ORIGINAL ARTICLE

Effects of Baicalin on Pharmacokinetics of Florfenicol and mRNA Expression of CYP1A2, CYP2C11, CYP3A1, UGT1A1, MDR1, and ABCC2 in Rats

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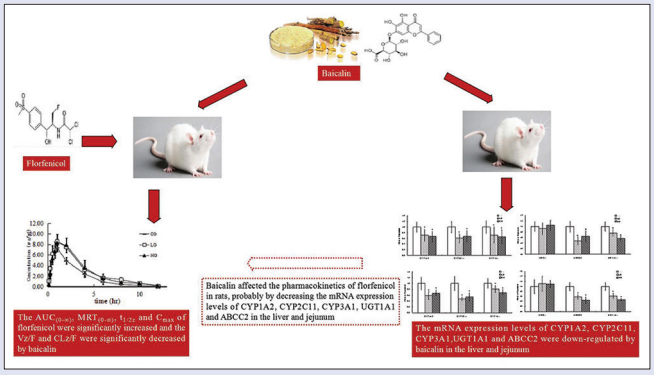
ABSTRACT

Background: The traditional Chinese medicine *Scutellariae radix* is often used in combination with antibiotics, such as florfenicol, in Chinese veterinary medicine. Baicalin (5, 6, 7-trihydroxyflavone-7-β-D-glucu ronide) is the main active constituent of *S. radix*. The effects of baicalin on the pharmacokinetics of florfenicol are not known. Thus, we have studied the effects of baicalin on florfenicol pharmacokinetics and the mRNA expression of drug-metabolizing enzymes/efflux transporters in rats. **Materials and Methods:** Sprague-Dawley rats were given baicalin (50 mg/kg BW or 100 mg/kg BW) or 0.9% sodium chloride solution by intragastric administration for 7 days. They were then fed florfenicol by intragastric administration (25 mg/kg BW) on the 8th day. Blood samples were collected at various times, and the plasma concentrations of florfenicol were estimated with ultra-high performance liquid chromatography. The mRNA expression levels of cytochrome P450 (CYP) CYP1A2, CYP2C11, CYP3A1, UDP-glucuronosyltransferase 1A (UGT1A), multidrug resistance 1, and ATP-binding cassette C2 (ABCC2) in the liver and jejunum were analyzed with a real-time polymerase chain reaction. **Results:** The area under the concentration-time curve from zero to infinity, mean residence time from zero to infinity, elimination half-life, and peak concentration of florfenicol were significantly increased and the apparent volume of distribution fraction of the dose absorbed and plasma clearance fraction of the dose absorbed were significantly decreased by baicalin; the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, UGT1A1, and ABCC2 were down-regulated by baicalin. **Conclusion:** Baicalin affected the pharmacokinetics of florfenicol in rats, increased the plasma concentration and residence time of florfenicol, probably by decreasing the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, UGT1A1, and ABCC2 in the liver and jejunum.

Key words: Baicalin, drug-metabolizing enzymes, efflux transporters, florfenicol, pharmacokinetics, traditional Chinese medicines

SUMMARY

- The effects of baicalin on florfenicol pharmacokinetics and the mRNA expression of drug-metabolizing enzymes /efflux transporters in rats were studied.
- Baicalin affected the pharmacokinetics of florfenicol in rats, increased the plasma concentration and residence time of florfenicol, probably by decreasing the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, UGT1A1, and ABCC2 in the liver and jejunum.



Abbreviations used: CG: Control group; LG: Low-dosage group; HG: High-dosage group; CY: Cytochrome; UGT: UDP-glucuronosyltransferase; MDR: Multidrug resistance; P-gp: p-glycoprotein; MRP: Multidrug resistance protein; ABC: ATP-binding cassette; RT-PCR: Real-time polymerase chain reaction; UHPLC: Ultra-high-performance liquid chromatography; $AUC_{(0-\infty)}$: Area under the concentration-time curve from zero to infinity; $MRT_{(0-\infty)}$: Mean residence time from zero to infinity; $t_{1/2}$: Elimination half-life; T_{max}: Time to reach peak concentration, Vz/F: Apparent volume of distribution fraction of the dose absorbed; CLz/F: Plasma clearance fraction of the dose absorbed; C_{max}: Peak concentration.

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INTRODUCTION

Veterinary herbal medicines have attracted interest because of the medicines' natural origin, lack of drug residue, and low frequency of side effects.[1] In veterinary practice, herbal medicines are widely used in combination with conventional drugs to prevent and control diseases. However, herbs contain phytochemicals that may interact with co-administered drugs, altering their pharmacokinetics and causing interactions by inducing or inhibiting drug-metabolizing enzymes and/or efflux transporters.[2] Therefore, it is imperative to assess these interactions, as they may affect clinical herb-drug interactions.[3]

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Florfenicol is a synthetic broad-spectrum antibiotic with activities like that of chloramphenicol; the drug is widely used to control bacterial infection in veterinary practice.[4-6] Florfenicol has low toxicity and better antibacterial activity than that of chloramphenicol or thiamphenicol.[7-9] The pharmacokinetics of florfenicol have been extensively studied in various animal species,[6,10-14] but there are few studies on the effects of drug-metabolizing enzymes or efflux transporters on the metabolism of florfenicol *in vivo*. Liu *et al*.[15] have reported that p-glycoprotein and/or cytochrome P450 (CYP) CYP3A are likely involved in the disposition of florfenicol in rabbits, and Wang *et al*.[16] have suggested that CYP 3A plays a key role in the pharmacokinetics of florfenicol in chickens.

Baicalin (5, 6, 7-trihydroxyflavone-7-β-D-glucuronide) is the main active constituent of *Scutellariae radix*, the root of *Scutellaria baicalensis* Georgi[17] [Figure 1]. It has been reported to have numerous pharmacological activities, including antioxidant, antiproliferative, antiviral, anti-inflammatory, and liver-protective properties.[18] In Chinese veterinary clinics, *S. radix* and its related traditional Chinese medicine preparations (e.g., Shuanghuanglian oral liquid) are commonly used to treat bacterial diseases in combination with other antibiotics, such as florfenicol, one of the most widely used veterinary antibiotics in animal husbandry. Thus, understanding the effects of baicalin on the pharmacokinetics of florfenicol and drug-metabolizing enzymes/efflux transporters can provide a reference for drug combination in clinical practice.

In this research, we have evaluated the effects of baicalin on the pharmacokinetics of florfenicol in rats by use of ultra-high performance liquid chromatography (UHPLC). In addition, the effects of baicalin on the mRNA expression of cytochrome P450 1A2 (CYP3A2), CYP2C11, CYP3A1, UDP-glucuronosyltransferase enzymes (UGT1A), multidrug resistance 1 (MDR1), and ATP-binding cassette C2 (ABCC2) in rat liver and jejunum were analyzed with real-time polymerase chain reaction (RT-PCR). We believe that the results may help predict the clinical effects of baicalin-florfenicol interactions.

MATERIALS AND METHODS

Chemicals and reagents

Baicalin was obtained from the National Institutes for Foods and Drug Control (Beijing, PR China). Florfenicol was supplied by Sichuan Dingjian Animal Pharmaceutical Co., Ltd., Chengdu, PR China. The drug was dissolved in polyethylene glycol 400 (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) to a concentration of 25 mg/ml for intragastric administration. Florfenicol and chloramphenicol (internal standard) analytical standards were obtained from China Institute of Veterinary Drug Control (Beijing, PR China). Acetonitrile and methanol were HPLC-grade (Merck Chemicals Ltd., Darmstadt, Germany). All other chemicals were of analytical grade or better and used as received.

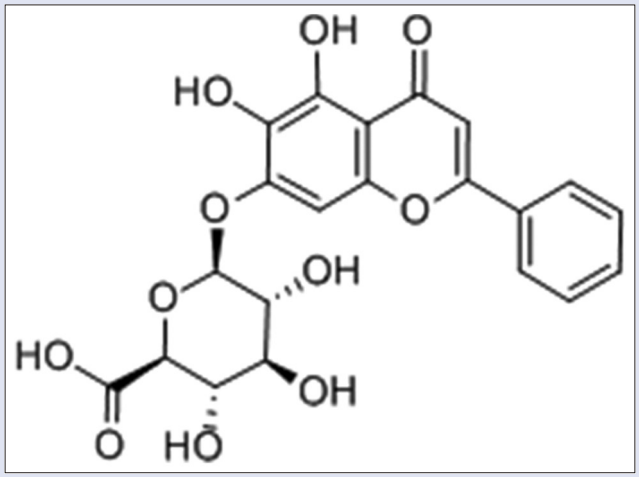

Figure 1: Chemical structure of baicalin

Animals

Male Sprague-Dawley rats (220 ± 20 g), license number SCXK2015-030, were obtained from Chengdu Dashuo Experimental Animal Co. Ltd., Chengdu, PR China. The animals were housed at the laboratory animal research center of Sichuan Animal Science Academy in house cages under standard laboratory conditions at a temperature of 22°C ± 2°C, with a natural light-dark cycle. The rats were fed a regular rodent diet and allowed free access to water during a 1-week acclimatization period before they were used for experiments. All efforts were made to minimize animal suffering. All experimental procedures and protocols in this study were reviewed and approved by the Animal Ethics Committee of Sichuan Animal Science Academy and were conducted in accordance with the principles outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.[19]

Ultra-high-performance liquid chromatography for detection of florfenicol in plasma

The analysis was performed on UltiMate 3000 HPLC (Thermo Fisher Scientific Inc., Chelmsford, MA, USA) as reported.[20] A Diamonsil C_{18} column (4.6 mm × 250 mm, 5 μm; Thermo Fisher Scientific Inc., Chelmsford, MA, USA) was used to simultaneously detect florfenicol and chloramphenicol at constant 40°C. The mobile phase consisted of acetonitrile and water (27:73, v: v) at a flow rate of 1.0 ml/min and an injection volume of 20 μl. The UV detector was set at 223 nm, and the overall run time of the analysis was 16 min.

Method validation was performed by the use of these variables: limit of detection (LOD), limit of quantification (LOQ), precision, extraction recovery, and correlation coefficients of the calibration curves.

LOD and LOQ were detected based on a signal-to-noise ratio of 3 and 10, respectively. The precision was estimated by intra-day and inter-day precision for 3 days at 3 standard levels (0.1, 2.5, and 20 μg/ml). The extraction recovery was expressed as the ratio of the mean area of florfenicol in plasma samples to that of the analytes in neat standard samples at equivalent concentrations. The standard curve of florfenicol was derived from the ratios of the peak-areas of florfenicol and the internal standard chloramphenicol (S) and plotting them against the corresponding concentration of florfenicol in blank plasma (C). The standard samples of florfenicol were prepared at concentrations of 50, 20, 10, 5.0, 2.5, 0.5, 0.1, 0.05 μg/ml, with each parallel processing five samples.

The effect of baicalin on pharmacokinetics of florfenicol in rats

Study design, formulation, and dosage regimen

Thirty rats were randomly assigned to 1 of 3 equal groups (n = 10 per group), control group (CG); low-dosage group (LG, 50 mg baicalin/kg BW); and high-dosage group (HG, 100 mg baicalin/kg BW). All rats were given corresponding baicalin solution or the same volume of 0.9% sodium chloride solution by intragastric administration once each morning for 7 days.

Pharmacokinetic study

On the 8th day, after rats were fasted for 12 h, a suspension containing florfenicol (25 mg/kg) was given to all rats in each group by intragastric administration. Blood samples from each rat were collected through the oculi chorioideae vein at 0.083, 0.25, 0.50, 0.75, 1, 2, 4, 6, 8, 10, and 12 h

after the administration of florfenicol. Plasma samples were separated by centrifugation at 4000 rpm for 5 min and stored at −80°C until HPLC analysis.

Sample preparation

Plasma samples were prepared as we have described.[20] Briefly, a 100-μl aliquot of thawed plasma in a 2 ml centrifuge tube was spiked with 5 μg of chloramphenicol (internal standard) in 10 μl methanol and added to 400 μl of ethyl acetate. The tube was vortex mixed for 2 min, and the sample was centrifuged at 4000 rpm for 10 min at room temperature. The supernatant was transferred to a new tube, and the subnatant was re-extracted with 400 μl ethyl acetate solution to collect the extract again. The pooled supernatant was evaporated to dryness under a flow of nitrogen at 40°C. The residue was dissolved in 100 μl mobile phase and centrifuged at 12,000 rpm for 10 min at 4°C. Finally, 20 μl of the supernatant was injected into the UHPLC system for analysis.

The effect of baicalin on mRNA expression of CYP1A2, CYP2C11, CYP3A1, MDR1, ABCC2, and UGT1A1 in the liver and jejunum

Drug administration and sample collection

Twelve rats were randomly assigned to 1 of 3 equal groups (n = 4 per group). The study design, formulation, and dosage regimen are those in "*Effect of baicalin on pharmacokinetics of florfenicol in rats.*" On the eighth day, after being fasted for 12 h, rats were euthanized with anesthetic ether. Each liver and jejunum sample was removed quickly, perfused with ice-cold saline to remove blood residue, blotted dry, and stored at −80°C.

Total RNA isolation and synthesis of cDNA

Total RNA from each sample was isolated by the use of TRIzol reagent (Invitrogen Corporation and Applied Biosystems, Inc., Carlsbad, CA, USA) according to the manufacturer's protocol. Concentration, purity, and integrity of the total RNA samples were measured as reported.[20] Single-stranded cDNAs were synthesized from 5 μl RNA samples with RevertAid Premium Reverse Transcriptase (Thermo Fisher Scientific Inc., Chelmsford, MA, USA), using C100 PCR (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The products were stored at −80°C until analysis.

Real-time polymerase chain reaction analysis

RT-PCR was performed with the ABI StepOne RT-PCR (Applied Biosystems, Foster City, CA, USA) for a 20 μl reaction mixture that contained 10 μl High RoxSybrGreen qPCR Master Mix (Sangon Biotech (Shanghai) Co., Ltd., Shanghai, PR China), 2 μl cDNA, 0.4 μl of each oligonucleotide primer (10 μM), and 7.2 μl diethyl pyrocarbonate-treated autoclaved distilled water. All samples were run in duplicate. Cycling parameters used were these: initial denaturation at 95°C for 3 min followed by 40 cycles of denaturation at 95°C for 7 s, annealing at 55°C for 10 s, extension at 72°C for 15 s, and final extension at 72°C for 5 min. Glyceraldehyde-3-phosphate dehydrogenase was the house-keeping gene. The $2^{-(\Delta\Delta Ct)}$ method was used for the analysis of the data.[21] The data are represented as the fold change in gene expression relative to the control. The sequences of the forward and reverse primers are shown in Table 1.

Statistical analyses

The concentration-time profile of florfenicol was analyzed with Data Analysis System software (Chinese Pharmacological Society, Beijing, PR China). All data were presented as mean ± standard deviation. Statistical significant differences were evaluated between control and baicalin treatment groups by one-way ANOVA, using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). For all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Method validation for detection of florfenicol

The LOQ and LOD of florfenicol were validated at 0.06 and 0.02 μg/ml, respectively. The intra-day and inter-day assay precision at three standard levels was below 6.5%. The extraction recovery of three concentrations of florfenicol was more than 81.5%. The correlation coefficient (R^2) for the calibration curves was 0.9995 [Figure 2].

The effect of baicalin on pharmacokinetics of florfenicol

The effect of baicalin on pharmacokinetics of florfenicol in rats is presented in Table 2 and Figure 3. After intragastric administration of baicalin for 7 days, the area under the concentration-time curve from zero to infinity ($AUC_{(0-\infty)}$), mean residence time from zero to infinity ($MRT_{(0-\infty)}$), the elimination half-life ($t_{1/2z}$), and the peak concentration (C_{max}) of florfenicol in LG were significantly increased

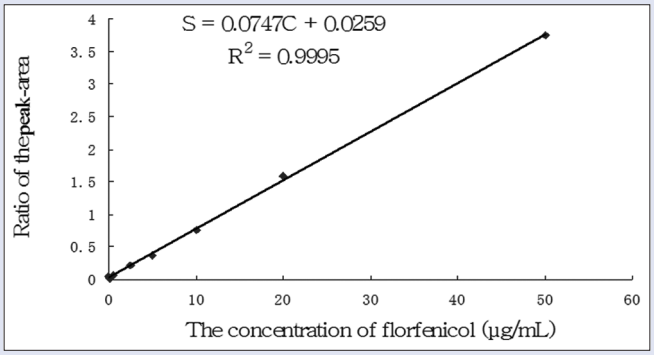

Figure 2: The standard curve of plasma florfenicol concentration. S: The ratios of the peak-areas of florfenicol and the internal standard (chloramphenicol); C: The corresponding concentration of florfenicol in blank plasma

Table 1: Sequences of the forward and reverse primers used for real-time reverse transcriptase - polymerase chain reaction

Enzymes	Forward	Reverse
CYP1A2	GAATGTCACCTCAGGGAATGC	GACCGCCATTGTCTTTGTAGTT
CYP2C11	GAGGACCATTGAGGACCGTATT	GGAGCACAGCCCAGGATAAA
CYP3A1	TTCCATCTTATGCTCTTCACCG	ACCTCATGCCAATGCAGTTC
MDR1	TCCTATGCTGCTTGTTTCCG	AGACTTTGGCCTTCGCGTA
ABCC2	ATACGAATCCAATCCTCTACCTGT	ATACGCCGCATAAGACCGA
UGT1A	CACGAAGTGGTGGTCATAGCA	TTTTGGAATGGCACAGGGTA
GAPDH	CAAGTTCAACGGCACAGTCAA	CGCCAGTAGACTCCACGACA

UGT1A: UDP-glucuronosyltransferase; MDR1: Multi-drug resistance 1; ABCC2: ATP-binding cassette; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase

Table 2: Pharmacokinetic characteristics of florfenicol in plasma of rats after intragastric administration of florfenicol (25 mg/kg BW) with or without baicalin (LG: 50 mg/kg BW for 7 days; HG: 100 mg/kg BW for 7 days) pretreatment (*n*=6, mean±standard deviation)

Characteristic	CG	LG	HG
$AUC_{(0-\infty)}$ (mg/l*h)	23.868±4.115	35.471±3.775*	34.357±4.233*
$MRT_{(0-\infty)}$ (h)	2.658±0.227	3.432±0.401*	3.266±0.215*
$t_{1/2z}$ (h)	1.403±0.109	1.717±0.263*	1.864±0.157*
T_{max} (h)	0.938±0.125	0.875±0.250	1.250±0.500
Vz/F (l/kg)	2.170±0.208	1.734±0.212*	1.875±0.152*
CLz/F (l/h/kg)	1.073±0.200	0.711±0.083*	0.737±0.097*
C_{max} (mg/l)	7.788±0.241	8.689±0.368*	8.370±0.182*

*Significantly different from CG, $P<0.05$. CG: Control group; LG: Low-dose group; HG: High-dose group; AUC: Area under the curve; MRT: Mean resistance time; $MRT_{(0-\infty)}$: Mean residence time from zero to infinity; T_{max}: Time to reach peak concentration; Vz/F: Apparent volume of distribution fraction of the dose absorbed; CLz/F: Plasma clearance fraction of the dose absorbed; $t_{1/2}$: Elimination half-life; C_{max}: Peak concentration; $AUC_{(0-\infty)}$: Area under the concentration-time curve from zero to infinity

(by 48.61%, 29.12%, 22.38%, and 11.57%, respectively), and the apparent volume of distribution fraction of the dose absorbed (Vz/F) and the plasma clearance fraction of the dose absorbed (CLz/F) were significantly decreased (by 20.09% and 33.74%, respectively) compared with corresponding values in CG. The $AUC_{(0-\infty)}$, $MRT_{(0-\infty)}$, $t_{1/2z}$ and C_{max} of florfenicol in HG were significantly increased (by 43.95%, 22.87%, 32.86%, and 7.47%, respectively), and the Vz/F and CLz/F were significantly decreased (by 13.59% and 31.31%, respectively) compared with corresponding values in CG. The time to reach peak concentration in LG and HG was not significantly different from corresponding values in CG.

The effect of baicalin on mRNA expression of CYP1A2, CYP2C11, CYP3A1, MDR1, ABCC2, and UGT1A1 in the liver and jejunum

The effects of baicalin on the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, MDR1, ABCC2, and UGT1A1 in the liver are presented in Figures 4 and 5. After intragastric administration of baicalin for 7 days, the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, ABCC2, and UGT1A1 in LG were significantly decreased to 0.71-fold, 0.61-fold, 0.72-fold, 0.48-fold, and 0.77-fold of levels in CG, respectively. The mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, ABCC2, and UGT1A1 in HG were significantly decreased to 0.52-fold, 0.67-fold, 0.76-fold, 0.65-fold, and 0.57-fold of levels in CG, respectively. The mRNA expression level of MDR1 in the two treatment groups was not significantly different from the level in CG.

The effects of baicalin on the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, MDR1, ABCC2, and UGT1A1 in the jejunum are presented in Figures 6 and 7. After intragastric administration of baicalin for 7 days, the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, ABCC2, and UGT1A1 in LG were significantly decreased to 0.58-fold, 0.47-fold, 0.69-fold, 0.58-fold, and 0.62-fold of levels in CG, respectively. The mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, ABCC2, and UGT1A1 in HG were significantly decreased to 0.51-fold, 0.64-fold, 0.53-fold, 0.45-fold, and 0.47-fold of levels in CG, respectively. The mRNA expression level of MDR1 in the two treatment groups was not significantly different from the level in CG.

DISCUSSION

CYP450 is the most important phase I metabolic enzyme. It plays a dominant role in the metabolism of endogenous compounds and

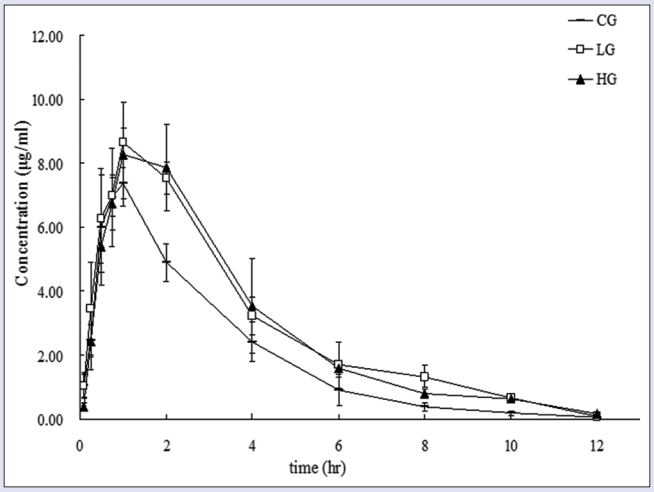

Figure 3: Mean plasma concentration-time profiles of florfenicol in rats after intragastric administration of florfenicol (25 mg/kg BW) with or without baicalin (LG, low-dosage group: 50 mg/kg BW for 7 days; HG, high-dosage group: 100 mg/kg BW for 7 days) pretreatment. Each symbol with a bar represents the mean ± standard deviation of concentrations for 6 rats. CG: Control group

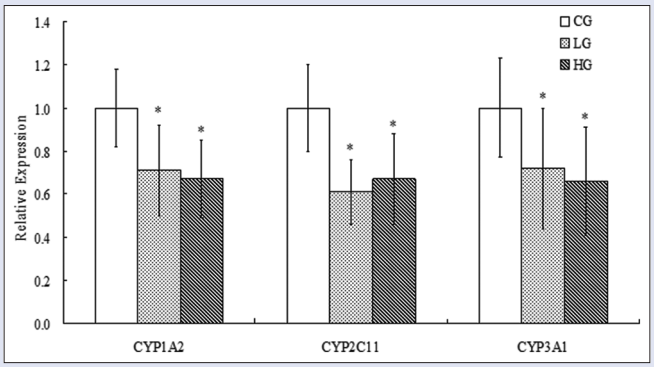

Figure 4: The effect of baicalin (LG, low-dosage group: 50 mg/kg BW for 7 days; HG, high-dosage group: 100 mg/kg BW for 7 days) on mRNA expression of CYP1A2, CYP2C11, CYP3A1 in rat liver (n = 6). *Significantly different from CG, P < 0.05. CG: Control group; CYP: Cytochrome P450

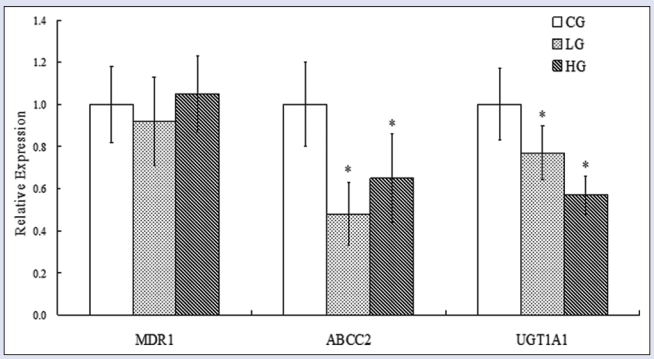

Figure 5: The effect of baicalin (LG, low-dosage group: 50 mg/kg BW for 7 days; HG, high-dosage group: 100 mg/kg BW for 7 days) on mRNA expression of multidrug resistance 1, ABCC2 and UGT1A1 in rat liver (n = 6). *Significantly different from CG, P < 0.05. CG: Control group

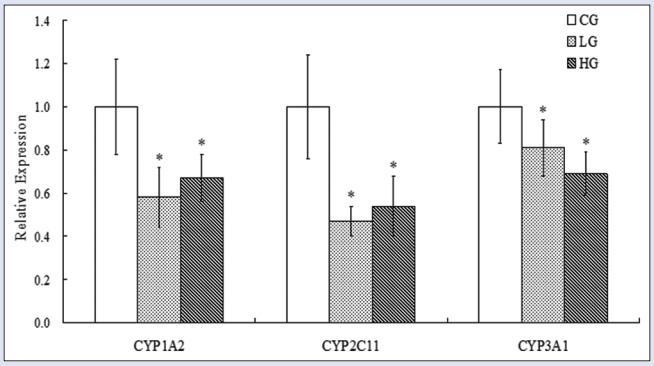

Figure 6: The effect of baicalin (LG, low-dosage group: 50 mg/kg BW for 7 days; HG, high-dosage group: 100 mg/kg BW for 7 days) on mRNA expression of CYP1A2, CYP2C11, CYP3A1 in rat jejunum (n = 6). *Significantly different from CG, $P < 0.05$. CG: Control group; CYP: Cytochrome P450

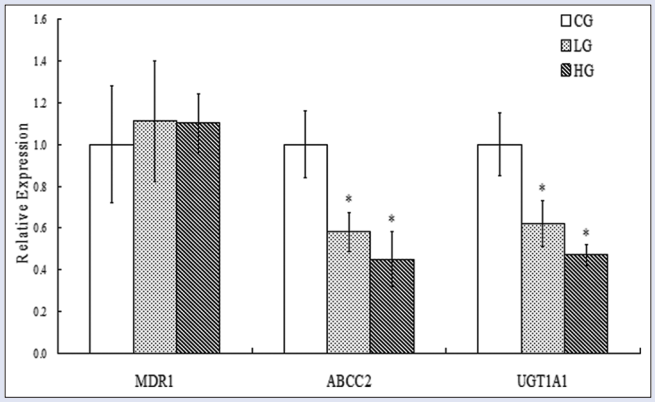

Figure 7: The effect of baicalin (LG, low-dosage group: 50 mg/kg BW for 7 days; HG, high-dosage group: 100 mg/kg BW for 7 days) on mRNA expression of multidrug resistance 1, ABCC2 and UGT1A1 in rat jejunum (n = 6). *Significantly different from CG, $P < 0.05$. CG: Control group

xenobiotics. Among the CYP450 subfamily, CYP1A2, CYP2C9, and CYP3A4 are the important CYP enzymes.[22] Rat CYP1A2, CYP2C11, and CYP3A1/2 are theoretically homologous to human CYP1A2, CYP2C9, and CYP3A4, respectively.[23-25] The UGT superfamily consists of enzymes that are responsible for a major biotransformation phase II pathway: the glucuronidation process.[26] In the present study, after 7-day intragastric administration of baicalin (50 mg/kg and 100 mg/kg), the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, and UGT1A were decreased, which may inhibit the activities of the corresponding enzymes, thus leading to down-regulation of the metabolism of florfenicol. Thus, the residence time of florfenicol *in vivo* was increased, which was consistent with the pharmacokinetic results ($MRT_{(0-\infty)}$ in LG and HG were significantly increased by 29.12% and 22.87%, respectively; CLz/F were significantly decreased by 33.74% and 31.31%, respectively). In the liver, multidrug resistance protein 2 (MRP2; encoded by ABCC2) is at the canalicular (apical) surface of hepatocytes, where it transports endogenous and xenobiotic substrates and potentially excretes them into bile. In our study, the mRNA expression levels of ABCC2 in baicalin-treated rats were significantly decreased, which may have inhibited the activities of hepatic MRP2, reducing the efflux of florfenicol. Thus, the plasma concentration of florfenicol was increased, which was also approximately in accordance with the pharmacokinetic results ($AUC_{(0-\infty)}$ in LG and HG were significantly increased by 48.61% and 43.95%, respectively).

Although several studies have been conducted on the effect of baicalin on drug metabolic enzymes, the dosages, administration routes, or experimental animal species from each other were different, and their results varied or were even opposed. Gao *et al.*[17] reported that baicalin inhibited the activity of CYP1A2 after intravenous injection of baicalin in rats at the dose of 450 mg/ml for 3 days.[17] Multiple doses of baicalin (0.90 g/kg, intravenously, once daily for 7 days) in rats significantly decreased the expression of hepatic CYP3A2. In addition, baicalin competitively inhibited midazolam (as a probe used to determine CYP3A4/5 activity) metabolism in rat liver microsomes in a concentration-dependent manner.[18] Baicalin inhibited intestinal CYP3A activity and protein expression in rats after oral administration of baicalin at the dose of 5, 10, 20, and 200 mg/kg for 7 days.[27] In addition, baicalin competitively inhibited CYP3A activity in rat liver microsomes in a concentration-dependent manner.[28] However, other studies had discrepant results regarding the effects of baicalin on CYP enzyme activities. Li *et al.*[29] reported that baicalin had no effect on either CYP3A4 or MDR1 gene expression of HepG2 cells *in vitro*. In addition, it has been reported that baicalin exposure significantly increased the hepatic expression of CYP1A1/2 after intra-abdominal injection of baicalin in mice at the dose of 80 mg/ml and 160 mg/ml for 3 days.[30] Considering these results, the baicalin dosage used clinically, and the conversion of the dose between human and rat, we chose 50 mg/kg as low dosage and 100 mg/kg as high dosage for 7 consecutive days of treatment to re-evaluate the effect of baicalin on the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, UGT1A1, and ABCC2 in rats.

CONCLUSION

We evaluated the effects of baicalin (the major active constituent of *S. radix* in traditional Chinese medicines) on the pharmacokinetics of the antibiotic florfenicol and mRNA expression of CYP1A2, CYP2C11, CYP3A1, MDR1, ABCC2, and UGT1A1 in rats. Baicalin affected the pharmacokinetics of florfenicol, increased the plasma concentration and residence time of the drug, probably by decreasing the mRNA expression levels of CYP1A2, CYP2C11, CYP3A1, UGT1A1, and ABCC2 in the liver and jejunum. The results of these experiments in rats should prompt studies on the effects of *S. radix* used in conjunction with various pharmaceuticals in veterinary medicine.

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Conflicts of interest

There are no conflicts of interest.

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