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Application of a liquid chromatography/tandem mass spectrometry method to pharmacokinetic study of mangiferin in rats

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ABSTRACT

A simple, rapid and accurate liquid chromatography–electrospray ionization-tandem mass spectrometry method was developed and validated for quantification of mangiferin in rat plasma. After the addition of the internal standard (IS) paracetamol, plasma samples were pretreated by protein precipitation. Chromatographic separation was carried out on a C_{18} column by isocratic elution with methanol–acetonitrile–1% acetic acid (40:3:57, v/v/v). The detection was performed on a Sciex API 3000 LC/MS/MS with TurboIonSpray ionization (ESI) inlet in the positive ion MRM mode. Good linearity was achieved over the concentration range of 3.01–601 ng/mL. Intra- and inter-day precisions were less than 9.1%, and accuracy ranged from 100.5% to 104.0%. The pharmacokinetic profiles of free mangiferin at three dose levels and mangiferin in Zhimu decoction and Zhimu–Huangbai decoction were studied for the first time in rats by this method. After single intragastric administration of free mangiferin 17.5, 35 and 70 mg/kg, C_{max} and AUC increased but non-proportional to the doses. At the same dose level (35 mg/kg), C_{max} and AUC of mangiferin in two decoctions were significantly higher than the corresponding values of free mangiferin.

1. Introduction

Herb-pairs (*Yaodui* or *Duiyao* in Chinese), the basic composition units of Chinese herbal formulas, usually consist of two Traditional Chinese Medicine (TCM) herbs. Zhimu–Huangbai herb-pair is a famous formula composed of Zhimu (*Rhizoma Anemarrhenae*) and Huangbai (*Cortex Phellodendri*). In the clinical practice of TCM, this herb-pair is frequently used for treating seminal emission, eczema with itching, febrile diseases with high fever, diabetes due to internal heat and constipation. Mangiferin (1,3,6,7-tetrahydroxyxanthone-C-2-β-D-glucoside, Fig. 1) is one of the main active flavonoid components of *Rhizoma Anemarrhenae*. Extensive studies indicate that mangiferin has a variety of pharmacological effects including antioxidant [1], antidiabetic [2], antibacterial [3], antitumor [4], hepatoprotective [5], neuroprotective [6], and gastroprotective [7] actions.

The pharmacokinetics of mangiferin has been studied in rats following intravenous administration [8–10]. Unfortunately, little information is available related to the pharmacokinetics after oral administration. Wang et al. [11] determined the pharmacokinetics in rats after oral administration of mangiferin 120 mg/kg. Han et al. [12] estimated the oral bioavailability of mangiferin to be only 1.2%. The pharmacokinetic profiles of mangiferin following different single oral dose and dose proportionality of the plasma levels have not been fully characterized yet. In addition, the pharmacokinetic differences of mangiferin in Zhimu decoction and Zhimu–Huangbai decoction compared with free mangiferin have not been investigated. The elucidation of the differences is important to the rational clinical application of Zhimu–Huangbai herb-pair.

Development of a rapid, sensitive, and reliable method to determine mangiferin in plasma is a prerequisite to the pharmacokinetic evaluation. Earlier publications have described methods for mangiferin determination in biological samples mainly using HPLC–UV [11,13–15]. There exist some limitations of these methods including long run time, large volumes of biological samples, and inadequate sensitivity. Recently, Suryawanshi et al. [10] developed a liquid chromatography tandem mass spectrometry (LC–MS/MS) method for simultaneous analysis of mangiferin and four glycosides in plasma with the long chromatographic run time (12 min), which was unsuitable for analyzing large numbers of plasma samples obtained from pharmacokinetic studies. Han et al. [12] reported a method to determine mangiferin in rat plasma by UPLC–MS/MS. However, the method was not sensitive enough with LLOQ of 20 ng/mL. In the present study, a novel rapid and sensitive LC/MS/MS method has been developed and validated for quantification of mangiferin in rat plasma. Using the established method, the pharmacokinetic behaviors of mangiferin at three dose levels and mangiferin in Zhimu decoction and Zhimu–Huangbai

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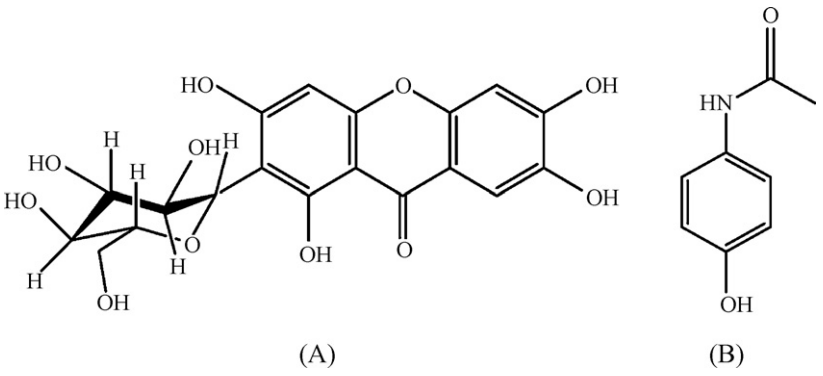

Fig. 1. Chemical structures of (A) mangiferin and (B) paracetamol (internal standard).

decoction were investigated for the first time in rats following intragastric administration.

2. Experimental

2.1. Chemicals and reagents

Mangiferin standard (purity > 98%) was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Paracetamol (purity > 99%) as the internal standard (IS) was provided by Shanghai Winherb Medical S & T Development Co., Ltd (Shanghai, China). Methanol, acetonitrile and acetic acid were of HPLC grade and purchased from Fisher Scientific (Fairlawn, NJ, USA) and Tedia Company (Fairfield, OH, USA), respectively. HPLC-quality water was prepared using a Milli-Q plotwater purification system (Millipore, Bedford, MA, USA). Other chemicals were of analytical grade.

2.2. Herbal materials and contents of mangiferin in Zhimu–Huangbai decoction and Zhimu decoction

Zhimu (*Rhizoma Anemarrhenae*) and Huangbai (*Cortex Phellodendri*) were purchased from Guangdong Kangmei Pharmaceutical Co., Ltd (Puning, Guangdong, China). The mixture (200 g) of Zhimu and Huangbai (1:1, w/w) was extracted thrice by refluxing with boiling water for 1 h, then the solution was filtered and concentrated to obtain the Zhimu–Huangbai decoction. Zhimu (100 g) decoction was prepared as the same procedure described above. To calculate the administration dosage, the contents of mangiferin in the decoctions were quantitatively determined by ultra performance liquid chromatography (UPLC) method, which was a modified version of a previously published method [16]. The contents of mangiferin were 2.24 and 3.79 mg/mL in Zhimu–Huangbai decoction and Zhimu decoction, respectively.

2.3. LC/MS/MS instrument and conditions

Chromatographic analysis was performed using an Agilent 1100 series LC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a G1311A quaternary pump, a vacuum degasser unit, and a G1313A autosampler. Room temperature was controlled at 20 °C by air conditioner. Separation of the analytes from plasma was achieved on a CAPCELL PAK C_{18} column (150 × 2.0 mm i.d., 5 μm, Shiseido, Japan) with a SecurityGuard C_{18} guard column (4 × 2.0 mm i.d., Phenomenex, Torrance, CA, USA) at room temperature. The isocratic mobile phase was composed of methanol–acetonitrile–1% acetic acid (40:3:57, v/v/v) at a flow-rate of 0.25 mL/min.

Mass spectrometric detection was performed on an API 3000 triple-quadrupole mass spectrometer (AB Sciex Instruments, USA). A TurboIonSpray interface operating in positive ionization mode was used. The turbo-gas temperature was set at 500 °C and the ionspray voltage was adjusted to 4500 V. High purity nitrogen served as nebulizer gas (NEB, GAS1, 12), curtain gas (CUR, 9), collision gas (CAD, 8) and auxiliary gas (AUX, GAS2, 7 L/min). The mass spectrometer was operated at unit resolution for both Q1 and Q3 in the multiple reaction monitoring (MRM) mode, with a dwell time of 100 ms per MRM channel. Focusing potential (FP), entrance potential (EP), collision cell exit potential (CXP), and declustering potential (DP) were set at 270, 10, 20, and 40 for both the analyte and IS. The optimized fragmentation transitions for MRM were m/z 423.0 → 327.1 with collision energy (CE) of 27 for mangiferin, and m/z 152.2 → 110.2 with CE of 25 for IS. Analyst 1.4 software was used for the control of equipment, data acquisition and analysis.

2.4. Preparation of standard and quality control (QC) samples

Standard stock solutions of mangiferin (200.4 μg/mL) and the IS (404 μg/mL) were separately prepared by dissolving the accurately weighed reference compounds in methanol and in 50% methanol. Working solutions for calibration and controls were prepared by appropriate dilution with 40% methanol. The IS working solution (404 ng/mL) was obtained by diluting its stock solution with 50% methanol. All these solutions were stored at 4 °C and brought to room temperature before use.

The calibration sample at highest concentration of 601 ng/mL for mangiferin was prepared by adding the working solution (20.04 μg/mL) 0.15 mL to blank plasma 4.85 mL. Then this sample was serially diluted with blank plasma to obtain other calibration samples at concentrations of 3.01, 6.01, 10.0, 30.1, 60.1, 100, and 301 ng/mL. The calibration curves were prepared and assayed along with QC samples and each batch of rat plasma samples. The QC samples were prepared at three different concentration levels of 6.01 (low), 60.1 (mid), and 541 ng/mL (high) together with the dilution QC (1002 and 4008 ng/mL) samples. QC samples were prepared in drug-free plasma from a second set of mangiferin stock and working solutions. All calibration and QC samples were divided into aliquots in eppendorf tubes (2 mL) and stored at −75 °C until analysis.

2.5. Sample preparation

To each 200 μL plasma sample, 50 μL of IS working solution (404 ng/mL) was added. After vortex mixing for 10 s, 600 μL of acetonitrile–acetic acid (9:1, v/v) was added and the mixture was vortexed for 2 min. Following centrifugation for 10 min at 13,000 rpm, the supernatant was transferred to another tube

and evaporated to dryness at 35 °C under a nitrogen stream. The residue was dissolved in 200 μL of mobile phase, and vortex-mixed for 1 min. A 20-μL aliquot of the solution was injected into the LC/MS/MS for analysis.

2.6. Method validation

To investigate the selectivity of the method, blank plasma samples from six different sources were pretreated and analyzed. The chromatogram of each blank plasma sample was compared with that of the corresponding plasma sample spiked with mangiferin and IS. The response of mangiferin at the concentration of the lower limit of quantitation (LLOQ) should be at least 5 times more than that of the baseline noise.

Linearity was assessed by assaying calibration curves in plasma at eight concentration levels ranging from 3.01 to 601 ng/mL in three separate runs. And the curves were fitted by a weighted ($1/x^2$) least-squares linear regression method through the measurement of the peak-area ratio of the analyte to IS. The acceptance criterion for a calibration curve was a correlation coefficient (r) of 0.99 or better, and that each back-calculated standard concentration must be within 15% deviation from the nominal value except at LLOQ, for which the maximum acceptable deviation was set at 20%. The LLOQ was defined as the lowest concentration in the standard curve at which the relative standard deviation was within 20% and accuracy was within 100 ± 20%, and it was established using five samples independent of standards.

Accuracy and precision of the method were evaluated by analyzing QC samples at three concentration levels (6.01, 60.1 and 541 ng/mL) in five replicates on three validation days. The assay accuracy was expressed as (observed concentration/nominal concentration) × 100%. Intra- and inter-day precision was obtained by one-way analysis of variance (ANOVA) testing and was expressed as relative standard deviation (RSD). The accuracy was required to be within 85–115%, and the precisions not to exceed 15%. Dilution QC samples (1002 and 4008 ng/mL) were assayed to ensure that dilution of study samples did not affect accuracy and precision. The dilution QC samples were diluted at ratio of 1:10 and 1:40 with blank plasma prior to analysis and processed as other QC samples.

The extraction recoveries of mangiferin and IS were determined at three QC levels (five samples each) by comparing the peak area of each analyte in spiked plasma samples with those of analytes in samples prepared by spiking extracted drug-free plasma samples with the same amounts of analyte at the step immediately prior to chromatography.

As far as the stability of mangiferin in rat plasma was concerned, there was no significant degradation observed under the storage conditions described in the previous reports [10,12]. In this study we just investigated the bench stability, freeze/thaw stability and the stability of mangiferin in reconstituted samples (auto-injector stability). Bench stability was assessed by leaving the QC samples at room temperature for 4 h. QC samples after two freeze–thaw cycles were analyzed for evaluating the freeze/thaw stability. The processed ready-to-inject samples were left in the autosampler vials at ambient temperature for 4 h to evaluate the stability of mangiferin in reconstituted samples. All the stability studies were conducted at three QC levels with five replicates for each.

2.7. Pharmacokinetic study

Sprague–Dawley rats (230–270 g) were obtained from Guangdong Provincial Experimental Animal Center. All animals were housed under controlled conditions (20–25 °C, RH 40–70%) with a natural light–dark cycle for 1 week. The studies were approved by the Animal Ethics Committee of Guangdong Provincial Hospital of TCM. The rats were fasted for 16 h before administration while water was taken *ad libitum*. The formation for intragastric administration of mangiferin was prepared by mixing mangiferin with 0.4% carboxymethyl cellulose sodium (CMC-Na) aqueous solution. Zhimu–Huangbai decoction and Zhimu decoction were prepared as described in Section 2.2 and were directly administered to rats. All rats were randomized into five groups (six in each group): mangiferin 17.5, 35 and 70 mg/kg body weight groups, Zhimu decoction and Zhimu–Huangbai decoction groups (the dose was 35 mg mangiferin/kg body weight). After a single dose was administered by oral gavage, blood samples (0.5 mL) were collected in heparinized tubes via the orbital vein at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 h. All blood samples were centrifugated at 3000 rpm for 10 min to collect plasma. The plasma obtained were stored at −75 °C until analysis. To obtain the pharmacokinetic parameters of mangiferin, the concentration–time data were analyzed by non-compartmental methods using the DAS 2.1.1 software program (Clinical Drug Evaluating Center, Anhui, China). The peak plasma drug concentration (C_{max}) and time to C_{max} (T_{max}) were obtained directly from the detected concentration *vs* time data.

3. Results and discussion

3.1. Method development

In order to develop ESI conditions, mangiferin was dissolved in methanol, and was infused into the mass spectrometer to carry out quadrupole full scans in positive ion mode at first. The ion $[M+Na]^+$ at m/z 445.5 was the main peak with highest signal intensity in the spectra, but we found that the ion was not stable in the following test. When mangiferin and IS was injected directly into the mass spectrometer along with the mobile phase, the analytes yielded predominantly $[M+H]^+$ ions at m/z 423.0 for mangiferin and at m/z 152.2 for IS. Each of the precursor ions was subjected to collision-induced dissociation to determine the resulting product ions. From the product ion mass spectra in Fig. 2, the most abundant fragment ions were generated at m/z 303.3 for mangiferin and m/z 110.2 for IS, respectively. At first, we used the fragment ion at m/z 303.3 as product ion to measure mangiferin in plasma, but high chemical background noise was observed. The chromatographic peak of mangiferin at LLOQ concentration was interfered by endogenous compounds and submerged in the baseline noise, which led to poor sensitivity. Consequently, the second abundant fragment ion at m/z 327.1 was taken into consideration. As far as we observed, very low background was obtained when monitoring the ion at m/z 327.1. So the mass transitions chosen for quantitation were m/z 423.0 → 327.1 for mangiferin and m/z 152.2 → 110.2 for IS.

The chromatographic conditions, especially the composition of the mobile phase, were optimized through several trials to achieve good chromatographic behavior and appropriate ionization for mangiferin and IS. In this method, plasma sample was pretreated by simple protein precipitation. Matrix effect (ME) was observed to obviously decrease the response of the analytes. To avoid or reduce the ion suppression, the proportion of organic phase in the mobile phase was decreased, but the run time was significantly prolonged. Suryawanshi et al. [10] delayed the retention time of mangiferin and the total analysis time to 6.07 min and 12.0 min, respectively, to eliminate completely the matrix suppression. Finally, considering the speed and sensitivity, we employed methanol–acetonitrile–1% acetic acid (40:3:57, v/v/v) as the mobile phase. The MEs under the optimized LC/MS/MS conditions were evaluated by comparing the peak areas of mangiferin from the spike-after-extraction samples (the blank plasma samples were from six different sources) to those obtained for the standards in mobile phase at equivalent concentrations. Although the ion suppression still existed (the ratios were 45.2 ± 0.6% at low concentration and 43.9 ± 0.9% at high concentration), the analysis was speeded up, mangiferin and IS were detected

Table 1
Accuracy and precision for the analysis of mangiferin in QC samples ($n = 3$ days, five replicates per day).

Added concentration (ng/mL)	Found concentration (mean ± SD) (ng/mL)	Accuracy (%)	Precision (%)	
			Intra-day RSD	Inter-day RSD
6.01	6.21 ± 0.45	103.2	6.9	9.1
60.1	60.4 ± 2.5	100.5	4.0	4.8
541	562 ± 24	104.0	3.4	7.8

at retention times of 2.20 and 1.80 min, respectively, and the LLOQ was 3.03 ng/mL which was sensitive enough for the pharmacokinetic study of mangiferin.

3.2. Method validation

3.2.1. Specificity

The specificity of the method was evaluated by analyzing individual blank plasma samples from six different sources. All samples were found to have no interferences from endogenous substances at the retention time of either the analyte or the IS. Typical chromatograms of a blank plasma, a spiked plasma sample with mangiferin and IS, and a plasma sample from a rat are shown in Fig. 3.

3.2.2. Calibration curve, linearity and LLOQ

The method exhibited good linearity over the concentration range of 3.01–601 ng/mL with correlation coefficients $r > 0.994$. A typical equation of the calibration curve was: $y = 1.09 \times 10^{-3}x + 6.52 \times 10^{-4}$ ($r = 0.9977$), where y is the peak-area ratio of mangiferin to IS and x is the plasma concentration of mangiferin.

The LLOQ for mangiferin was established at 3.01 ng/mL, which was sensitive enough for pharmacokinetic study of mangiferin in rats. The precision and accuracy at this concentration level was acceptable, with 5.5% of the RSD and 99.2% of the accuracy.

3.2.3. Accuracy and precision

The intra- and inter-day precision and accuracy of the assay were investigated by analyzing QC samples (6.01, 60.1 and 541 ng/mL). All the values are shown in Table 1. Intra-day RSD was below 6.9% and inter-day RSD was below 9.1%. The accuracy was within 100.5–104.0%. The method was proved to be highly accurate and precise.

To assess the accuracy and precision of dilution, five replicates dilution QC samples were prepared at each concentration of 1002 and 4008 ng/mL, and diluted 10- and 40-fold, respectively. The precision (RSD) was 1.5% and 3.8%, and the accuracy was 99.1% and 90.3%, demonstrating that samples can be accurately determined after dilution when the measured concentration of a sample is above the standard curve.

3.2.4. Recovery and stability

In the present study, the clean-up of the plasma samples was achieved through a simple and fast single-step protein precipitation procedure. Different kinds of extraction procedures, including liquid–liquid extraction (LLE) with ethyl acetate, ethyl acetate–ether, n-hexane–ethyl acetate, etc., were tried during our method development, but they were limited by low or unrepeated extraction recoveries for analyte. Finally the method of protein precipitation with acetonitrile–acetic acid (9:1, v/v) that has been reported in literature [11] was used, although this processing procedure yielded obvious matrix effect. The extraction recoveries of mangiferin were 72.0 ± 3.7%, 70.8 ± 2.5% and 81.8 ± 3.5% at three concentrations of 6.01, 60.1 and 541 ng/mL, respectively, while the recovery of the IS was 87.5 ± 1.1%. These results suggested that the recovery of mangiferin and the IS was consistent and was not concentration-dependent.

It was previously reported that mangiferin in plasma appeared to be stable when stored at −50 °C for at least 30 days [10] and −20 °C for 15 days [12]. The mean recoveries of QC samples were 93.9–105.6% for three different concentrations, which indicated that mangiferin was stable in plasma samples at room temperature for at least 4 h. Plasma samples were also stable over two

Table 2
Stability data of mangiferin in plasma QC samples ($n = 5$).

Added concentration (ng/mL)	Recovery (%)		
	Bench stability	Freeze/thaw stability	Autoinjector stability
6.01	95.2 ± 4.0	97.5 ± 5.9	96.4 ± 4.0
60.1	93.9 ± 4.2	94.4 ± 4.0	99.5 ± 7.7
541	105.6 ± 2.1	102 ± 1.7	95.1 ± 2.8

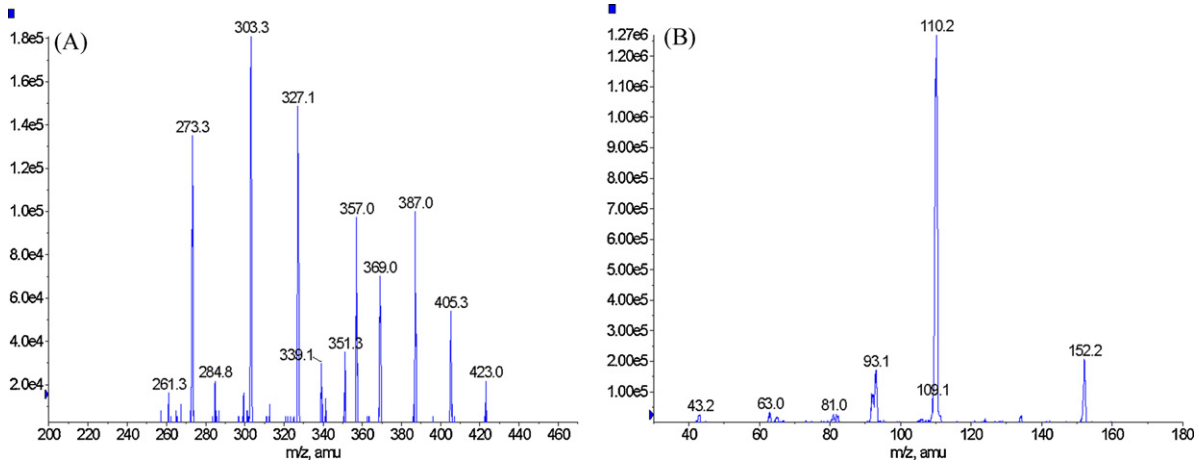

Fig. 2. Product ion mass spectra of the $[M+H]^+$ ions of (A) mangiferin and (B) IS.

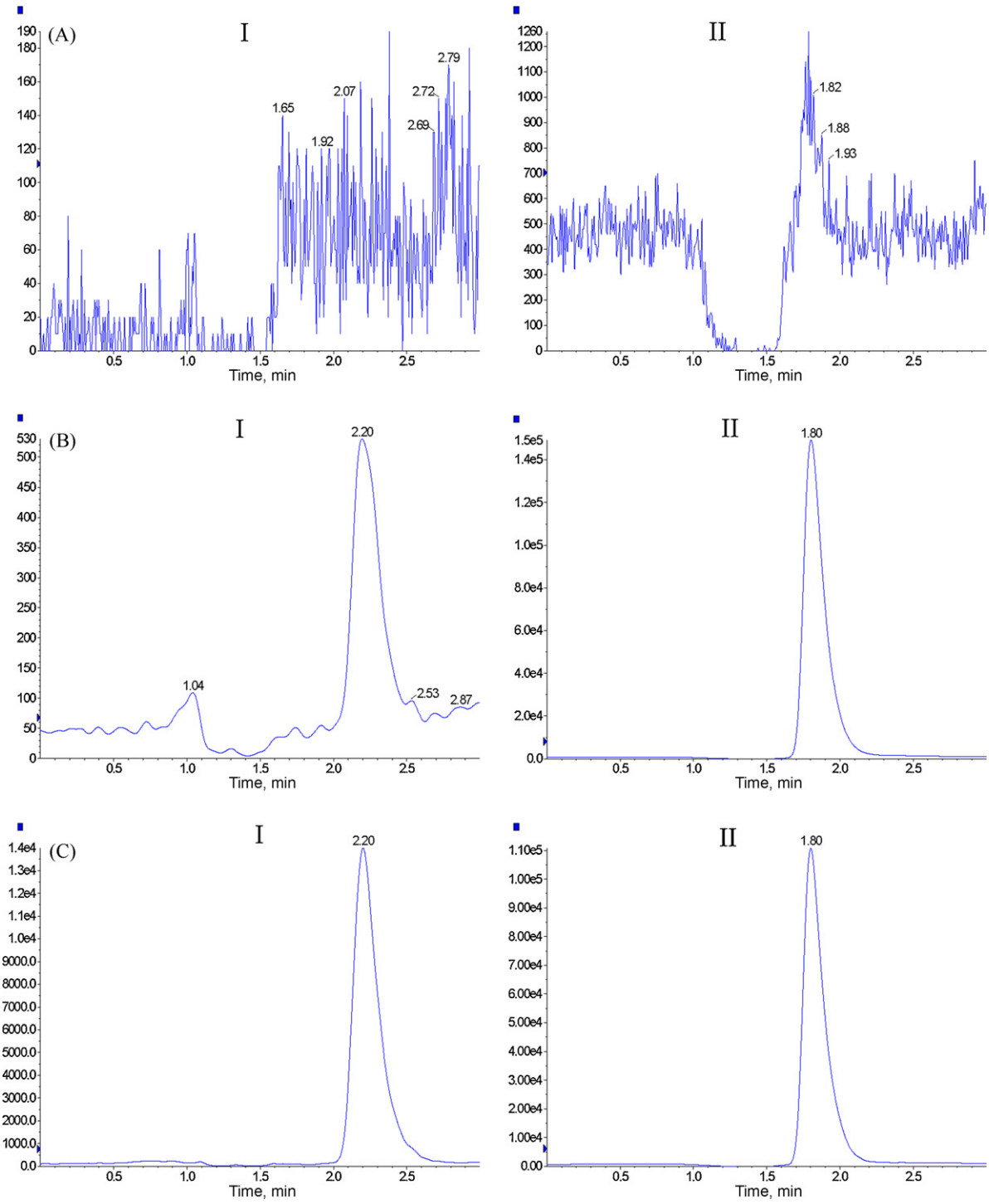

Fig. 3. Representative MRM chromatograms of (A) blank plasma; (B) blank plasma spiked with mangiferin (3.01 ng/mL) and IS; and (C) plasma obtained from a rat 4 h after an intragastric administration of mangiferin 17.5 mg/kg. I: mangiferin (m/z 423.0 → 327.1); II: IS (m/z 152.2 → 110.2).

freeze–thaw cycles in terms of mean recoveries. Mangiferin in the ready-to-inject samples was stable at room temperature for at least 4 h with no significant loss. The stability data are shown in Table 2. Taking all the points into consideration, mangiferin can be stored and processed under routine laboratory conditions without special attention.

3.3. Pharmacokinetic study

After single intragastric administration of free mangiferin 17.5, 35 and 70 mg/kg, the plasma mangiferin concentrations were successfully determined by using the LC/MS/MS method described above. The mean plasma concentration *vs* time profiles for mangiferin are presented in Fig. 4. High concentration level of mangiferin could be detected at only 0.25 h after administration, which indicated that mangiferin was absorbed very rapidly in rats. In addition, the pharmacokinetic differences were compared among free mangiferin, mangiferin in Zhimu decoction and mangiferin in Zhimu–Huangbai decoction at the dose level of 35 mg/kg. Fig. 5 shows the profiles of the mean mangiferin plasma concentration *vs* time. The data demonstrates that there is significant individual difference between the rats. The major phar-

Table 3
Main pharmacokinetic parameters of mangiferin in rats following intragastric administration of mangiferin 17.5, 35 and 70 mg/kg body weight, Zhimu decoction and Zhimu–Huangbai decoction.

Parameter	Mangiferin			Zhimu decoction	Zhimu–Huangbai decoction
	17.5 mg/kg	35 mg/kg	70 mg/kg		
C_{max} (μg/mL)	0.119	0.149	0.190	21.52	16.26
T_{max} (h)	1.00	1.00	0.25	3.00	4.00
$t_{1/2Z}$ (h)	2.34	3.41	5.10	1.46	1.65
AUC_{0-t} (μg h/mL)	0.428	0.626	0.753	122.4	94.36
$AUC_{0-\infty}$ (μg h/mL)	0.462	0.672	0.983	122.5	94.38
$MRT_{0-\infty}$ (h)	3.30	4.41	7.60	4.95	6.47

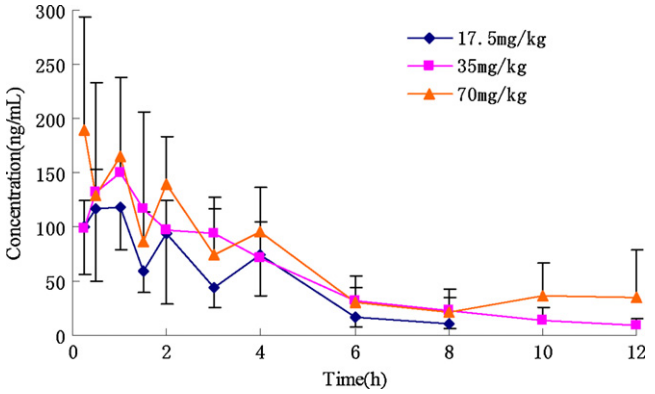

Fig. 4. Mean plasma concentration–time curves of mangiferin in rats following single intragastric administration of free mangiferin 17.5, 35 and 70 mg/kg body weight ($n = 6$, mean ± SD).

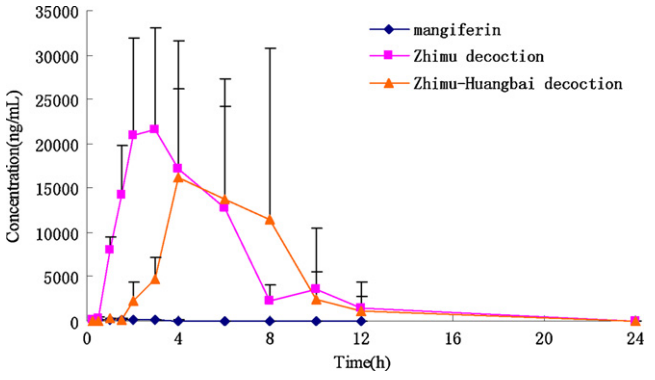

Fig. 5. Mean plasma concentration–time curves of mangiferin in rats following intragastric administration of free mangiferin, Zhimu decoction and Zhimu–Huangbai decoction (the dose was 35 mg mangiferin/kg body weight, $n = 6$, mean ± SD).

macokinetic parameters were calculated by non-compartmental method and are listed in Table 3.

Over the free mangiferin dose range studied, mean C_{max} and AUC increased but non-proportional to the doses. The values of $t_{1/2Z}$ seemed to be dose-dependent and ranged from 2.34 to 5.10 h. The results indicated that the pharmacokinetics of free mangiferin do not fit the linear dynamic features in the dose range of 17.5–70 mg/kg. After oral administration of Zhimu decoction and Zhimu–Huangbai decoction, C_{max} and AUC of mangiferin were significantly higher than the corresponding values obtained following administration of free mangiferin 35 mg/kg. The times to reach C_{max} (T_{max}) were prolonged to 3.0 and 4.0 h, respectively. Between two decoction groups, the absorption of mangiferin was slightly inhibited when Zhimu was combined with Huangbai.

4. Conclusions

The optimized LC/MS/MS method was validated to guarantee a reliable determination of mangiferin in rat plasma. Good linearity over the range of 3.01–601 ng/mL, the high sensitivity, selectivity, precision, accuracy and short retention time make the whole method suitable for related pharmacokinetic studies. The LC/MS/MS assay was successfully applied to determine mangiferin in rat plasma, and the pharmacokinetic profiles of mangiferin were investigated for the first time in rats after single intragastric administration of free mangiferin 17.5, 35 and 70 mg/kg, Zhimu decoction and Zhimu–Huangbai decoction.

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