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Original Article

Pharmacokinetic studies of multi-bioactive components in rat plasma after oral administration of Xintiantai I extract and effects of guide drug borneol on pharmacokinetics

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ABSTRACT

Objective: To investigate the *in vivo* pharmacokinetic characteristics of 17 bioactive components including ginsenoside Rg1, Rb1, Rd, berberine, epiberberine, jatrorrhizine, palmatine, columbamine, coptisine, evodiamine, dehydroevodiamine, rutaecarpine, limonin, hyperin, curcumin, demethoxycurcumin and bisdemethoxycurcumin in rat plasma after oral administration of Xintiantai I extract powder (XI) and Xintiantai I without guide drug borneol extract powder (XI without borneol), and study the compatibility effects of guide drug borneol on the pharmacokinetics.

Methods: A UHPLC-MS/MS method was established and fully validated for the comparative pharmacokinetics of 17 bioactive components. The pharmacokinetics parameters of 17 bioactive components after oral administration of XI and XI without borneol were calculated by the software of DAS 3.0 and intercompared.

Results: The specificity, linearity, lower limit of quantification (LLOQ), precision, accuracy, extraction recovery rates, matrix effects, and stability of the UHPLC-MS/MS assay were good within the acceptance criteria from FDA guidelines. Guide drug borneol can significantly increase AUC of G-Rd, palmatine, hyperin, curcumin, demethoxycurcumin, bisdemethoxycurcumin and C_{max} of 16 bioactive components except for dehydroevodiamine ($P < 0.05$), decrease T_{max} of G-Rd, berberine, columbamin, coptisine, limonin and MRT of 17 bioactive components in XI group ($P < 0.05$).

Conclusion: Guide drug borneol enhanced the absorption of G-Rd, palmatine, hyperin, curcumin, demethoxycurcumin and bisdemethoxycurcumin.

1. Introduction

Traditional Chinese medicine (TCM) as one of the predominant application mode in clinics, is often used according to the rule of compatibility “Jun (Monarch) - Chen (Minister) - Zuo (Adjuvant) - Shi (Guider)”. TCM formula compatibility not only attributed to pharmacological and pharmacodynamic synergism, but also influenced components’ ADME (absorption, distribution, metabolism, and elimination) process (Yao et al., 2015; Zhang et al., 2015). In the TCM compatibility theory, monarch drug, minister drug, and adjuvant drug often played primary and adjuvant therapeutic effects and guide drug was usually used to guide the bioactive components to the focus and harmonize their effects.

Xintiantai I is a novel hospital preparation for the treatment of mild cognitive impairment and Alzheimer disease (Wu, Zhong, & Sun, 2010). It was predominantly composed of six herbal medicines including *Panax ginseng* C. A. Mey., *Coptidis Rhizoma*, *Euodiae Fructus*, *Cistanches Herba*, *Curcumae Longae Rhizoma*, and borneol. In view of the low water solubility, low intestinal permeability, active efflux transports, and/or high metabolism of the bioactive components in this prescription including ginsenosides, alkaloids and curcuminoids (Chen et al., 2011; Siviero et al., 2015), borneol as a “Guide drug” in this prescription can theoretically promote the absorption of bioactive components to produce better

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health benefits. Numbers of pharmacokinetic experiments about combination administration of borneol *in vivo* were performed currently. In Lai's study, borneol could enhance the intestinal absorption and inhibit the metabolism of salvianolic acids (Lai et al., 2011), while in Wang's study, borneol also enhanced the intestinal absorption and inhibited the metabolism of NGR1, GRg1, and GRe (Wang et al., 2013). Although a better pharmacokinetic effect has been observed for the combined administration of borneol than the single use of herbs, the underlying synergistic effect of Xintiantai I and borneol is still an enigma. In this research, we studied the possible PK parameters of 17 bioactive components mentioned above in rat plasma after oral administration of Xintiantai I extract and Xintiantai I without borneol extract to reveal their pharmacokinetic behavior and variation.

2. Materials and methods

2.1. Chemicals and reagents

Ginsenoside Rg1, Rb1, and Rd, berberine, epiberberine, jatrorrhizine, palmatine, columbamine, coptisine, evodiamine, dehydroevodiamine, rutaecarpine, limonin, hyperin, curcumin, demethoxycurcumin, bisdemethoxycurcumin and naringin (used as internal standard, IS) were purchased from Baoji Chenguang Biological Technology Co., Ltd. The purity of all compounds was higher than 98.0%. HPLC grade acetonitrile (Merck, KGaA, Darmstadt, Germany) and formic acid (Kermel Chemical Reagent Co., Ltd.) were used for UHPLC analysis. Deionized water was prepared with a Milli-Q ultra-pure Water System (Millipore, Bedford, MA, USA).

Panax ginseng (batch number: R0717615, Origin: Jilin), *Coptidis Rhizoma* (batch number: H3617112, Origin: Sichuan), *Euodiae Fructus* (batch number: W2517313, Origin: Hunan), *Curcumae Longae Rhizoma* (batch number: J2417312, Origin: Sichuan), *Cistanches Herba* (batch number: R0117613, Origin: Xinjiang), and borneol (batch number: 151207, Origin: Yunnan) were purchased from Guangdong Province Herbal Medicine Co., Ltd. (Guangzhou, China) and authenticated by Professor Ji Ma (Southern Medical University, Guangzhou, China).

2.2. Preparation of Xintiantai I extract powder and Xintiantai I without borneol extract powder

A total of 60 g of *Panax ginseng*, 60 g of *Coptidis Rhizoma*, 80 g of *Euodiae Fructus*, 120 g of *Cistanches Herba*, and 120 g of *Curcumae Longae Rhizoma* were immersed in 4400 mL of 70% ethanol (volume percent) for 30 min, refluxing for 1.5 h and filtered. The residue was refluxed again with same solvent for 1.0 h and filtered. Twice filtration was merged, and concentrated by reducing pressure and dried by vacuum to obtain extract powder. Borneol (1.5 g) was dissolved in 95% ethanol, inclosed by beta-cyclodextrin and dried by vacuum to obtain borneol inclusion. Half of the extract powder and borneol inclusion were mixed evenly to obtain Xintiantai I extract powder. The other half extract powder was added with the same weight of beta-cyclodextrin to obtain Xintiantai I without borneol extract powder. To calculate the dosage employed in section "animal treatment", the content of 17 bioactive components in Xintiantai I extract powder and Xintiantai I without borneol extract powder were quantitatively determined. As a result, Xintiantai I extract powder and Xintiantai I without borneol extract powder dissolved into a solution with a concentration of 0.4 g/mL and 0.34 g/mL will be almost with equivalent bioactive components' content.

2.3. Animal treatment

A total of 12 adult male Wistar rats weighing 250–300 g were purchased from the Experimental Animal Center of Southern Medical University (License No. 44002100002118, Guangzhou, China) and housed under environmentally controlled conditions (25 ± 2) °C, relative humidity (50 ± 5)% with a 12-h light/dark cycle. All experimental procedures on animals were conducted in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animals in China.

All rats were divided into two groups randomly: Xintiantai I extract powder group ($n = 6$) and Xintiantai I without borneol extract powder group ($n = 6$). The rats in two groups were given the same dose of 4.5 mL/kg corresponding extracted powder respectively. Blood samples were collected from orbital plexus of eye at 0.17, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24 h after administration. Plasma was separated by centrifugation at 4500 r/min for 10 min and then transferred to clean tubes. All plasma samples were stored at −20 °C until analysis.

2.4. Blood sample preparation

Rat plasma samples (100 μL) were thawed to room temperature, added with 20 μL naringin (4.00 μg/mL) and vortex-mixed for 30 s. After vortex-mixing, 20 μL 2% (volume percent) HCl solution and 800 μL ethyl acetate-n-butyl alcohol mixture (6:4, volume percent) were added to the plasma. The sample was vortex-mixed for 3 min and centrifuged at 13,000 rpm for 10 min at 4 °C. The supernatant was then transferred into another Eppendorf tube and dried under nitrogen gas. The lower solution was added with 800 μL ethyl acetate-n-butyl alcohol mixture (6:4, volume percent) and repeated the same extraction procedure with the supernatant obtained. The supernatant was transferred into the former dried supernatant and dried under nitrogen gas. The residue was re-extracted in 100 μL methanol by vortex-mixing for 1 min and centrifuged at 13,000 r/min for 15 min at 4 °C. The supernatant was transferred to an auto sampler vial for analysis.

2.5. UHPLC-MS/MS analytical method

Separation and quantification of the analytes were achieved according to the UHPLC-MS/MS conditions in our previous work (Zeng et al., 2018) with some modifications. Chromatographic analysis was performed on a 1290 UHPLC system (Agilent Technologies, Inc., USA) and a 6410 triple-quadrupole mass spectrometery with an electrospray ionization source (ESI). Separation of the analytes was performed on a C_{18} column (Agilent® Zorbax Eclipse Plus, 4.6 mm × 150 mm, 3.5 μm) with the mobile phase consisted of acetonitrile (A) and 0.1% formic acid in water (B) at a flow rate of 0.5 mL/min. A gradient condition was applied with the following program: 0–1.5 min, 20%–25% (volume percent) A; 1.5–6.5 min, 25%–33% A; 6.5–9.0 min, 33%–50% A; 9.0–11.5 min, 50%–95% A; 11.5–13.0, 95%–20% A. The column temperature was maintained at 30 °C, and the injection volume was 5 μL.

All analytes were detected by using multiple reaction monitoring (MRM) in positive mode to monitor the precursor-to-product combination. The source parameters were set as follows: capillary voltage, 4000 V; MS heater temperature, 100 °C; drying gas flow, 8 L/min; Drying gas temperature, 340 °C; nebulizer pressure, 40 psi. The optimal precursor-to-product ion pairs, fragmentor, collision energy, and chemical structures for each analyte were shown in Fig. 1. All data acquisition and peak integration were performed using Qualitative Analysis B.04.00.

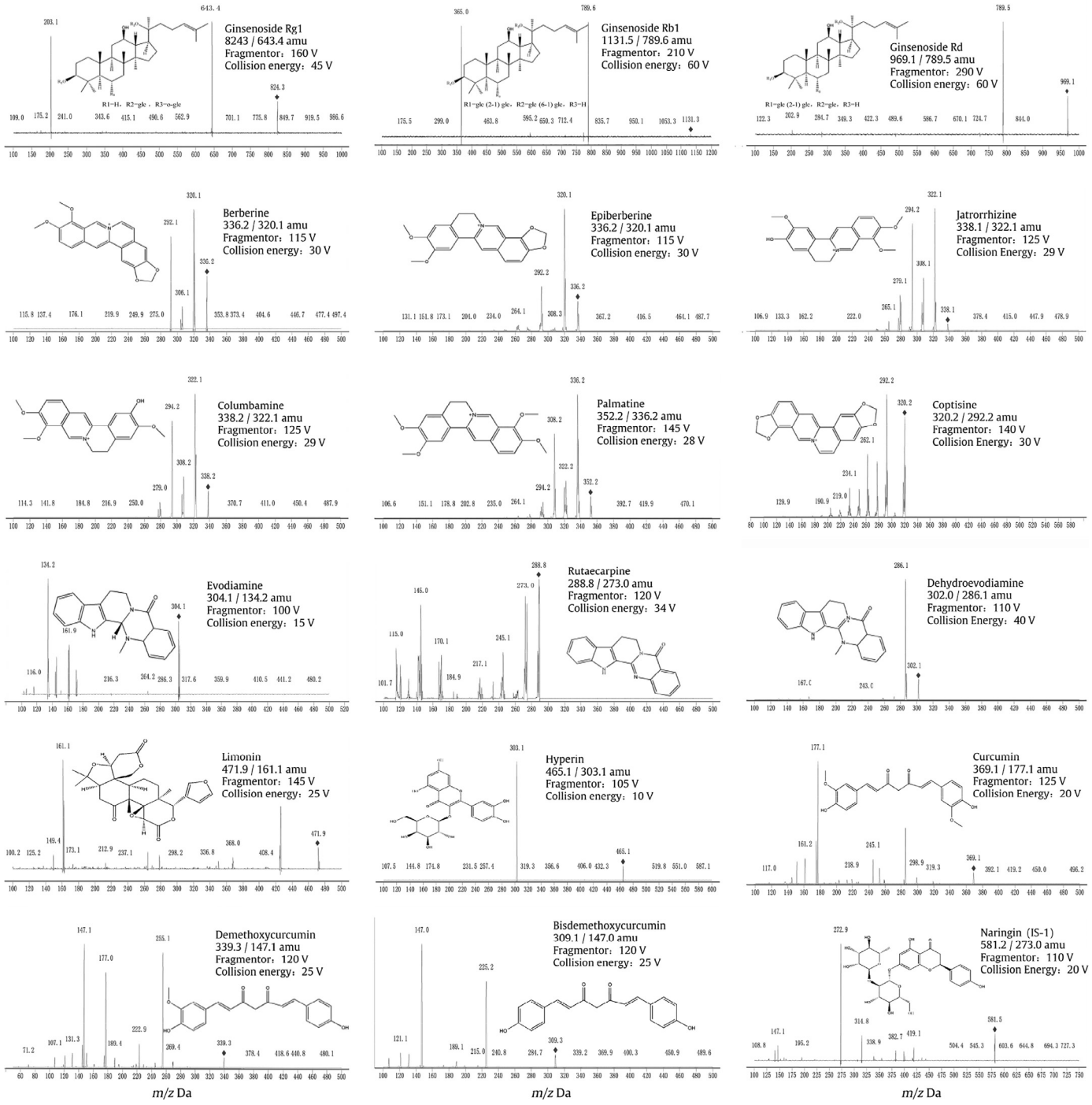

Fig. 1. Product ion scan spectra, fragmentor, collision energy, and chemical structures of 18 analytes.

2.6. Preparation of calibration standards and quality control (QC) samples

Stock solutions were prepared by accurately weighing and dissolving the above 17 standards in methanol. A mixed solution of these analytes was diluted to obtain a series of working standard solutions with finalt concentrations (ng/mL) range: Rg1, 2.020–505.0; Rb1 2.200–550.0; Rd, 2.034–508.5; berberine, 1.096–1096; epiberberine, 1.250–1250; jatrorrhizine, 1.072–1072; palmatine, 1.126–1126; columbamine, 1.232–1232; coptisine, 1.140–1140; evodiamine, 1.230–615.0; dehydroevodiamine, 1.000–500.0; rutaecarpine, 1.230–615.0; limonin, 1.080–540.0; hyperin, 1.008–504.0; curcumin, 1.260–630.0; demethoxycurcumin, 1.020–510.0 and bisdemethoxycurcumin, 1.011–505.5. Meanwhile, internal standard naringin was diluted to a final concentration of 4.00 μg/mL in the working solution. A total of 100 μL of the working solutions were spiked with blank rat plasma to obtain calibration standards and quality control (QC) samples. All solutions were stored at 4 °C before analysis.

2.7. Method validation

The previously developed method was validated for specificity, linearity, lower limit of quantification (LLOQ), precision, accu-

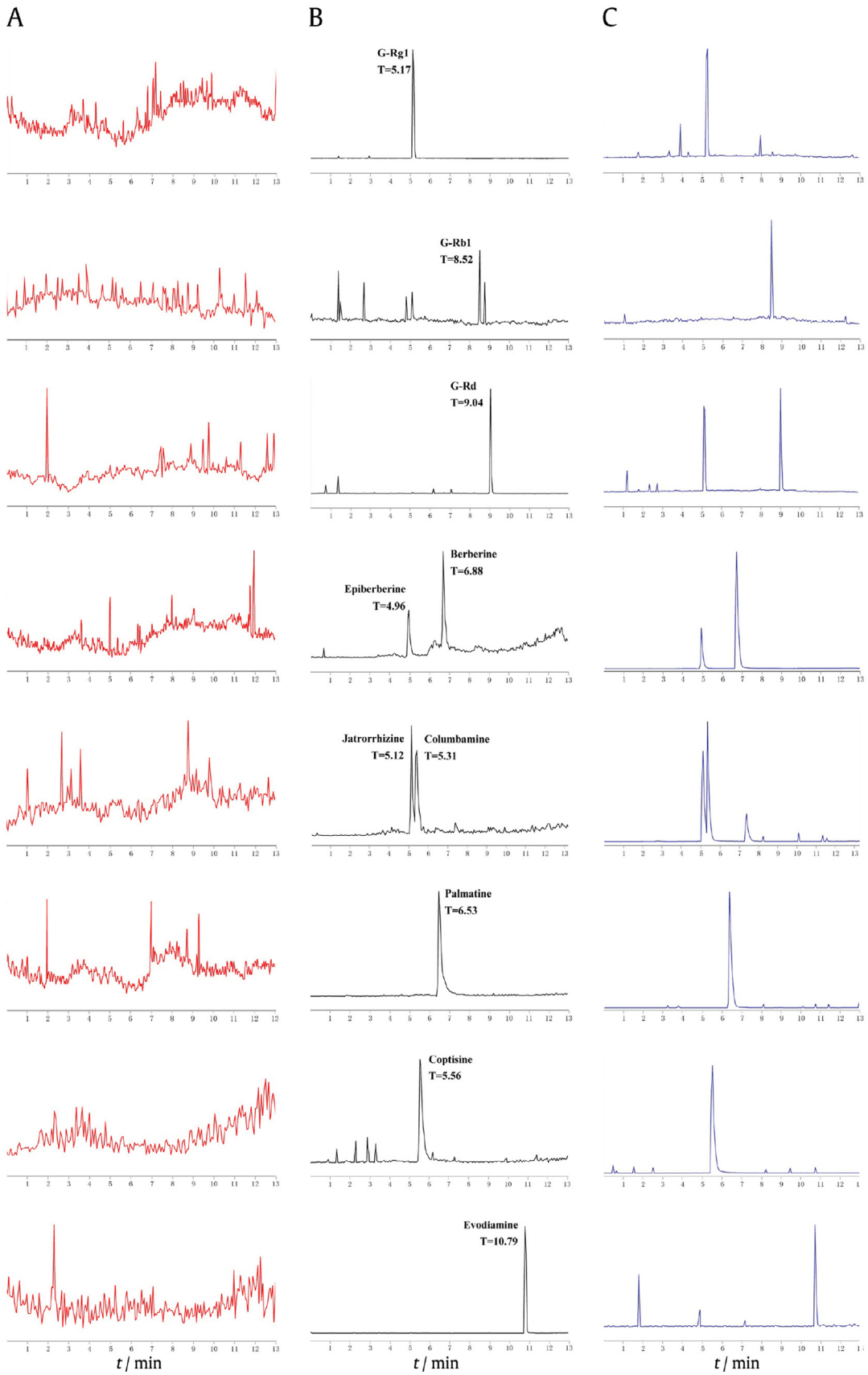

Fig. 2. Multiple reactions monitoring mode chromatograms of G-Rg1, Rb1, Rd, berberine, epiberberine, jatrorrhizine, palmatine, columbamine, coptisine, evodiamine, dehydroevodiamine, rutaecarpine, limonin, hyperin, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and naringin in blank plasma (A), blank methanol spiked with standards solution (B) and rat plasma sample after oral administration of Xintiantai 1 (C).

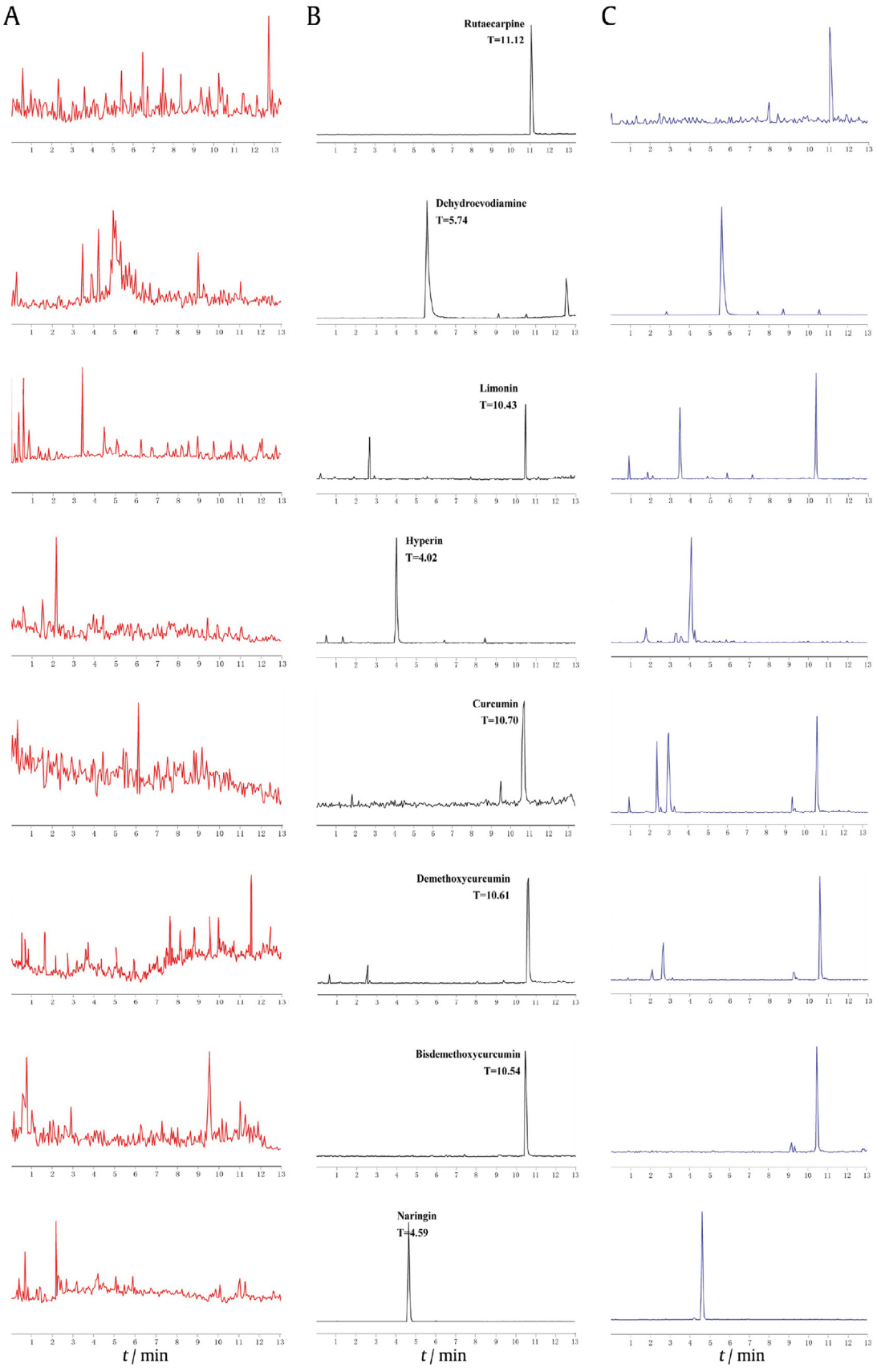

Fig. 2. Continued

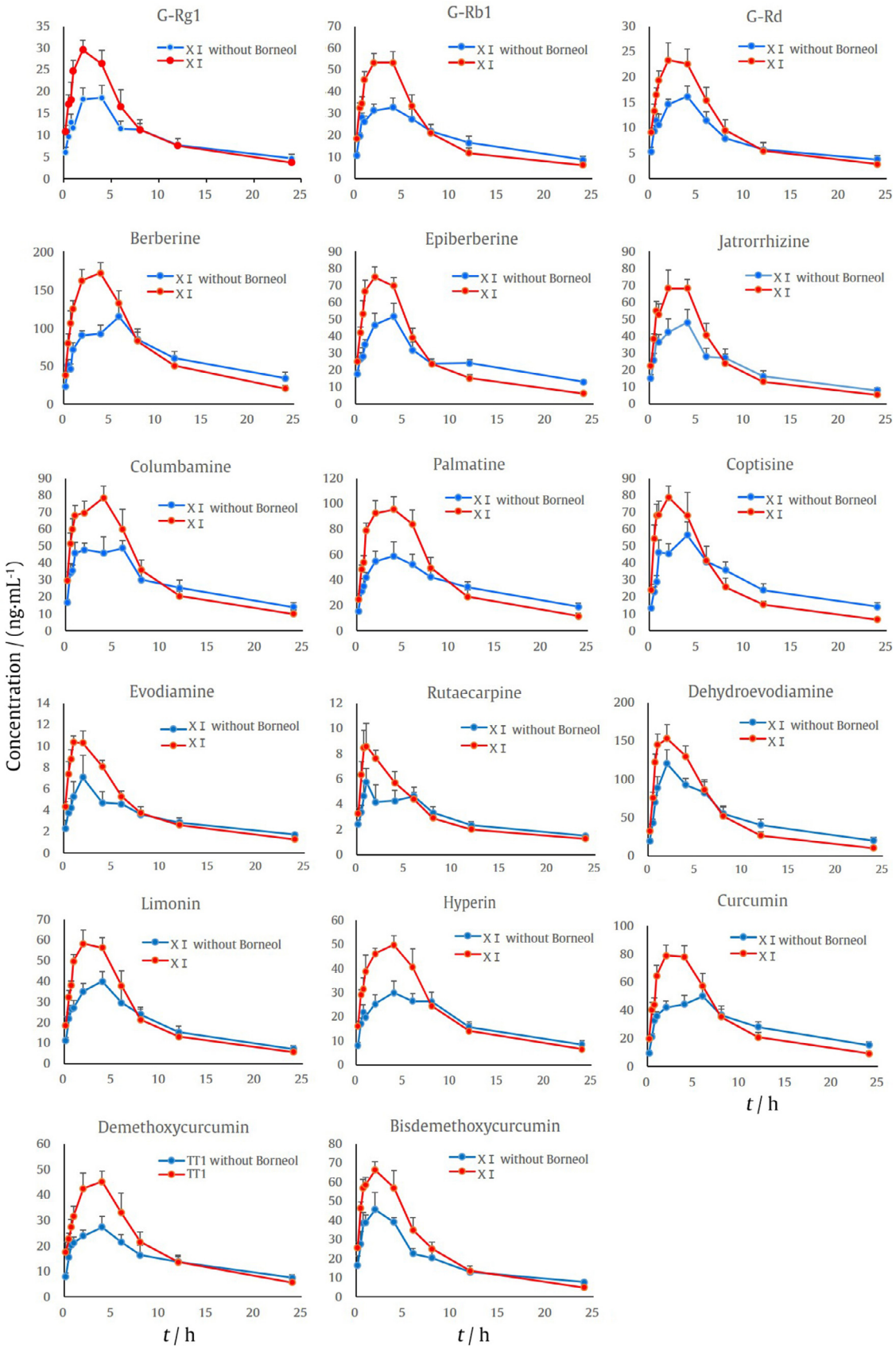

Fig. 3. Mean concentration-time profiles of G-Rg1, Rb1, Rd, and other compounds tested in rat plasma after oral administration of Xintiantai I extract and Xintiantai I without borneol extract (mean ± SD, $n = 6$).

Table 1
Summary of matrix effect, recovery, precision, and accuracy of all analytes for UHPLC–MS/MS method in rat plasma (mean ± SD, $n = 6$).

Analytes	Spiked conc. /(ng·mL^{-1})	Matrix effect/%	Recovery/%	Precision (RSD/%)		Accuracy (RE/%)	
				Intraday	Interday	Intraday	Interday
	2.020	94.75 ± 7.69	92.11 ± 9.23	9.46	8.06	−7.83	−13.27
G-Rg1	20.20	98.37 ± 5.14	96.92 ± 5.53	6.26	5.07	−3.14	−5.16
	505.0	98.67 ± 4.51	97.15 ± 4.08	1.90	2.00	−2.14	−1.49
	2.200	95.87 ± 6.94	93.22 ± 10.35	5.91	10.69	−7.21	−12.97
G-Rb1	22.00	98.70 ± 4.73	94.74 ± 6.02	6.41	6.60	−1.47	−4.29
	550.0	97.21 ± 4.27	98.58 ± 5.62	1.99	2.62	−1.03	−2.09
	2.034	96.27 ± 8.25	95.42 ± 8.33	5.95	9.40	−13.79	−7.75
G-Rd	20.34	99.07 ± 5.34	94.66 ± 7.92	5.66	6.17	−3.38	−2.30
	508.5	98.36 ± 4.02	97.24 ± 5.33	2.65	2.41	0.13	−1.30
	2.192	98.31 ± 5.28	96.84 ± 6.37	4.33	4.47	−3.94	−4.66
Berberine	21.92	98.68 ± 3.60	100.17 ± 4.83	3.94	4.43	−3.18	0.30
	548.0	101.27 ± 3.81	98.37 ± 4.76	1.60	2.07	1.39	1.42
	2.500	96.64 ± 5.36	97.57 ± 6.15	4.85	5.80	3.44	2.17
Epiberberine	25.00	99.32 ± 4.30	97.24 ± 5.12	3.10	5.34	2.72	−1.22
	625.0	98.57 ± 3.16	102.41 ± 4.29	1.10	2.32	1.30	−1.21
	2.144	97.47 ± 6.46	95.25 ± 7.27	5.54	6.16	−4.75	−3.97
Jatrorrhizine	21.44	100.61 ± 4.47	95.76 ± 4.73	2.01	5.97	3.26	−2.53
	536.0	98.39 ± 3.23	99.52 ± 5.68	1.24	2.99	2.04	−1.26
	2.464	97.74 ± 5.68	95.83 ± 6.91	4.13	6.12	−5.13	−2.42
Columbamine	24.64	98.73 ± 4.08	98.48 ± 4.84	3.10	3.28	2.40	−2.13
	616.0	99.02 ± 3.75	97.52 ± 4.95	1.63	1.62	1.51	−0.53
	2.252	96.53 ± 6.37	94.68 ± 7.03	5.77	6.20	7.51	4.37
Palmatine	22.52	103.39 ± 4.76	97.24 ± 5.28	4.20	4.75	0.44	−4.53
	563.0	98.47 ± 3.57	98.53 ± 5.87	2.05	2.52	1.39	−1.04
	2.280	97.04 ± 6.89	94.73 ± 6.94	6.56	4.85	−4.34	−5.11
Coptisine	22.80	98.43 ± 5.49	96.71 ± 5.52	3.86	4.92	−2.93	−0.82
	570.0	100.36 ± 3.64	102.47 ± 4.38	1.45	2.59	2.48	−1.49
	2.460	97.34 ± 6.84	94.28 ± 7.24	6.23	7.21	3.36	4.07
Evodiamine	24.60	101.62 ± 4.83	97.84 ± 6.46	3.61	3.96	−0.57	−1.61
	615.0	99.06 ± 4.02	97.42 ± 4.60	1.60	3.23	1.78	−1.95
	2.460	96.36 ± 7.69	95.07 ± 8.92	6.20	7.57	−5.55	−10.78
Rutaecarpine	24.60	98.07 ± 5.63	99.61 ± 6.13	3.04	3.56	2.50	−1.86
	615.0	98.44 ± 3.87	98.25 ± 4.33	1.06	2.23	1.45	−1.55
	2.000	97.46 ± 6.83	94.72 ± 7.33	6.43	6.24	−6.30	−10.25
Dehydroevodiamine7	20.00	98.64 ± 4.71	98.42 ± 7.36	3.24	4.17	−3.27	−1.41
	500.0	101.34 ± 4.52	97.66 ± 4.18	1.27	2.08	1.50	−1.18
	2.160	96.58 ± 8.12	93.67 ± 10.59	8.49	8.59	−2.64	−4.25
Limonin	21.60	97.87 ± 4.84	97.48 ± 7.69	4.89	4.15	−1.23	1.79
	540.0	99.78 ± 4.76	102.34 ± 5.26	1.68	2.55	2.52	−1.20
	2.016	95.75 ± 7.95	92.63 ± 9.62	6.75	6.73	−12.88	−14.41
Hyperin	20.16	98.62 ± 4.93	105.28 ± 6.70	5.84	4.86	−0.64	−1.84
	504.0	97.87 ± 4.79	95.39 ± 5.65	1.74	1.71	−1.75	−1.54
	2.520	96.43 ± 8.66	92.73 ± 11.31	5.54	5.23	−10.52	−8.78
Curcumin	25.20	99.38 ± 6.54	96.18 ± 7.74	4.05	4.96	−4.90	−2.20
	630.0	98.09 ± 5.49	96.32 ± 5.87	1.69	1.87	1.91	−1.41
	2.040	94.83 ± 7.59	96.74 ± 9.25	5.88	7.01	−6.76	−7.44
Demethoxycurcumin	20.40	97.88 ± 5.84	95.87 ± 6.92	3.54	5.60	1.98	−2.97
	510.0	100.62 ± 4.74	102.54 ± 5.36	2.33	3.22	0.78	−1.65
	2.022	96.85 ± 8.37	93.38 ± 8.24	7.10	8.75	−9.63	−9.77
Bisdemethoxycurcumin	20.22	99.24 ± 4.59	96.69 ± 7.35	4.23	4.97	2.34	2.43
	505.5	98.62 ± 4.97	96.31 ± 5.37	1.18	2.22	−1.71	−1.16

racy, extraction recovery rates, matrix effects, and stability according to the FDA guidelines for the validation of bioanalytical methods.

2.8. Data analysis

The pharmacokinetic parameters (maximum concentration (C_{max}), the time to C_{max} (T_{max}), area under the curve (AUC), mean residencet ime (MRT), biological half-life time ($t_{1/2z}$) and clearance rate/bioavailability (CLz/F) were calculated by the non-compartmental analysis of plasma concentration *vs* time data using Drug and Statistics (DAS 3.0) software (BioGuider Co., Shanghai, China). All the pharmacokinetic parameters were statistically analyzed by SPSS 16.0 (SPSS Inc., Chicago, USA). A *P*-value less than 0.05 was considered statistically significant.

3. Results and discussion

3.1. Method validation

Under this developed UHPLC-MS/MS conditions, no interfering peaks were found at the retention times of the 17 analytes and IS in the chromatograms of blank plasma, blank plasma spiked with analytes and plasma sample after oral administration of Xintiantai I (Fig. 2). This method exhibited good specificity. All analytes exhibited good linearity with a relatively wide concentration range and the R^2 value was greater than 0.999. The LLOQ values were (ng/mL): 2.020 for G-Rg1, 2.200 for G-Rb1, 2.034 for G-Rd, 1.096 for berberine, 1.250 for epiberberine, 1.072 for jatrorrhizine, 1.232 for columbamine, 1.126 for palmatine, 1.140 for coptisine, 1.230 for evodiamine, 1.230 for rutaecarpine, 1.000 for dehydroevodiamine, 1.080 for limonin, 1.008 for hyperin,

1.260 for curcumin, 1.020 for demethoxycurcumin, and 1.011 for bisdemethoxycurcumin.

The matrix effect, recovery, precision, and accuracy of 17 analytes were investigated at three low-to-high concentrations and presented in Table 1. The RSD values for intra-day and inter-day precision of all analytes were less than 10.69%. The RE values for accuracy ranged from −14.41% to +7.51%. The matrix effect for all analytes was within the acceptable value ranged from 94.75% to 103.39%. The extraction recoveries ranged from 92.11% to 105.28%. The analytes were stable in plasma under four different storage conditions (Short-term (25 °C, 12 h), Long-term (−20 °C, 28 d), 3-freeze-thaw cycles and Post-preparation (25 °C, 12 h) with the precision and accuracy ranged from 1.73% to 12.78% and −13.78% to 7.85% respectively.

3.2. Pharmacokinetic data analysis

The validated method was successfully applied to pharmacokinetic studies of 17 analytes in rat plasma after oral administration of Xintiantai I and Xintiantai I without borneol. The mean plasma concentration-time profiles ($n = 6$) were shown in Fig. 3, and the pharmacokinetic parameters were presented in Table 2.

As showed in Fig. 3, the shapes of the concentration–time curve of all 17 analytes were markedly different between XI group and XI without borneol group. Compared with samples from groups given XI without borneol extracts, the time achieved peak concentration (T_{max}) for G-Rd, berberine, columbamine, coptisine and limonin were obviously earlier, meanwhile the peak plasma concentration (C_{max}) for all analytes except dehydroevodiamine were obviously higher in the plasma profile of XI group. Although the T_{max} and the C_{max} of the analytes were accelerated and increased to different degrees, only the area under the curve (AUC) of G-Rd, palmatine, hyperin, curcumin, demethoxycurcumin and bisdemethoxycurcumin were increased. This phenomenon suggested that the compatibility also may speed up the elimination of the analytes which indicated significantly shorter the mean residence time (MRT) for all 17 analytes in XI group compared with XI without borneol group.

As showed in Table 2, in comparison with Xintiantai I without borneol group, borneol can significantly increase AUC of G-Rd, palmatine, hyperin, curcumin, demethoxycurcumin, and bisdemethoxycurcumin and the C_{max} of 16 bioactive components except for dehydroevodiamine ($P < 0.05$); decrease T_{max} of G-Rd, berberine, columbamin, coptisine, limonin and MRT of all 17 bioactive components in Xintiantai I group ($P < 0.05$).

4. Discussion

The pharmacokinetic parameters of Xintiantai I, such as $t_{1/2z}$, T_{max}, C_{max}, AUC_{0-t}, MRT, CLz/F showed a difference compared with Xintiantai I without borneol.

Borneol, as “Guide drug” in the prescription, was usually used to guide the bioactive components of herbs to target site. Since the gastrointestinal tract is an important barrier for low oral bioavailability and P-glycoprotein (P-gp) is the main cause of this effect, Guide drug borneol can obviously improve the intestinal absorption by loosening the intercellular tight junction, increasing the number and volume of pinocytosis vesicles, inhibiting the function of P-glycoprotein (P-gp), and increasing the fluidity of membrane and the permeability of bilayer lipid membrane (Chen & Wang, 2004; He, Shen, & Li, 2011; Yu, Ruan, Dong, Yu, & Cheng,

Table 2
Pharmacokinetic parameters of 17 bioactive components after oral administration of Xintiantai I and Xintiantai I without borneol extracts (mean ± SD, $n = 6$).

Analytes	Group	AUC_{0-t} /(ng·mL^{-1}·h)	MRT_{0-t} / h	$t_{1/2z}$ / h	T_{max} / h	C_{max} / (ng·mL^{-1})	CLz/F / (L·h^{-1}·kg^{-1})
G-Rg1	XI without Borneol	226.77 ± 38.90	9.00 ± 0.52	13.95 ± 2.70	3.33 ± 1.03	19.27 ± 2.36	63.31 ± 10.283
	XI	275.11 ± 34.85	7.47 ± 0.48*	8.96 ± 3.37	2.33 ± 0.82	30.05 ± 2.02*	63.92 ± 10.04
G-Rb1	XI without Borneol	448.69 ± 53.33	9.03 ± 0.53	12.25 ± 1.11	4.33 ± 1.51	34.90 ± 3.42	33.72 ± 4.96
	XI	499.04 ± 65.23	7.13 ± 0.44*	4.16 ± 0.65*	3.00 ± 1.10	55.81 ± 4.66*	39.69 ± 4.39
G-Rd	XI without Borneol	182.97 ± 22.54	8.75 ± 0.51	10.51 ± 5.55	3.33 ± 1.03	16.53 ± 1.59	91.85 ± 23.23
	XI	223.23 ± 35.20*	7.24 ± 0.45*	5.06 ± 2.85*	2.17 ± 0.98*	24.39 ± 2.62*	87.97 ± 17.81
Berberine	XI without Borneol	1566.01 ± 190.77	9.66 ± 0.40	11.24 ± 3.51	5.67 ± 0.82	117.13 ± 14.34	9.92 ± 1.99
	XI	1759.83 ± 204.51	7.52 ± 0.32*	7.07 ± 1.40*	3.00 ± 1.10*	174.87 ± 11.85*	10.38 ± 1.06
Epiberberine	XI without Borneol	620.99 ± 65.14	9.23 ± 0.14	14.15 ± 2.10	3.33 ± 1.03	55.73 ± 3.86	22.55 ± 1.05
	XI	633.65 ± 76.43	6.67 ± 0.38*	8.49 ± 0.87*	2.33 ± 0.82	76.73 ± 5.07*	28.34 ± 1.99*
Jatrorrhizine	XI without Borneol	521.82 ± 81.84	8.19 ± 0.48	10.29 ± 1.74	3.33 ± 1.03	51.30 ± 5.55	31.63 ± 4.85
	XI	595.03 ± 69.64	6.59 ± 0.31*	5.16 ± 2.20*	3.00 ± 1.10	72.12 ± 7.31*	32.62 ± 2.84
Columbamine	XI without Borneol	690.38 ± 98.96	9.13 ± 0.42	13.64 ± 1.77	5.33 ± 1.03	52.81 ± 5.72	21.08 ± 3.35
	XI	792.79 ± 110.08	7.42 ± 0.31*	6.30 ± 2.89*	3.67 ± 0.82*	79.38 ± 6.89*	23.50 ± 1.70
Palmatine	XI without Borneol	868.19 ± 67.60	9.62 ± 0.39	13.40 ± 3.04	4.33 ± 1.51	62.76 ± 8.76	16.36 ± 1.98
	XI	1013.04 ± 110.44*	7.42 ± 0.33*	5.73 ± 2.47*	3.33 ± 1.03	100.31 ± 7.46*	18.73 ± 2.41
Coptisine	XI without Borneol	695.58 ± 84.50	9.121 ± 0.37	12.76 ± 2.00	3.67 ± 0.82	57.81 ± 6.89	21.15 ± 3.05
	XI	660.70 ± 97.87	6.69 ± 0.20*	6.43 ± 2.73*	2.33 ± 0.82*	80.64 ± 7.26*	28.63 ± 3.82*
Evodiamine	XI without Borneol	79.223 ± 17.53	9.21 ± 0.44	13.22 ± 3.33	1.67 ± 0.52	7.74 ± 1.22	188.21 ± 46.50
	XI	86.69 ± 23.80	6.44 ± 1.57*	7.88 ± 3.42	1.33 ± 0.52	10.92 ± 0.74*	200.82 ± 38.12
Rutaecarpine	XI without Borneol	67.90 ± 10.80	9.21 ± 0.39	13.95 ± 6.31	1.13 ± 0.44	6.39 ± 0.87	210.25 ± 31.09
	XI	64.45 ± 13.62	6.12 ± 1.80*	7.06 ± 3.33	0.88 ± 0.14	9.27 ± 1.36*	264.28 ± 43.27*
Dehydroevodiamine	XI without Borneol	1233.87 ± 152.49	8.32 ± 0.39	10.49 ± 3.28	2.33 ± 0.82	122.51 ± 15.52	13.43 ± 2.56
	XI	1242.15 ± 132.32	6.36 ± 0.44*	5.44 ± 2.36*	1.50 ± 0.55	158.23 ± 16.46	15.46 ± 1.46
Limonin	XI without Borneol	462.78 ± 62.88	8.41 ± 0.37	9.07 ± 2.00	4.33 ± 0.82	41.17 ± 4.70	36.73 ± 6.00
	XI	533.68 ± 75.51	6.90 ± 0.45*	7.75 ± 2.03	2.67 ± 1.03*	60.05 ± 4.54*	34.55 ± 5.11
Hyperin	XI without Borneol	433.12 ± 46.63	9.32 ± 0.34	10.98 ± 0.96	5.00 ± 1.67	31.71 ± 3.28	35.61 ± 4.50
	XI	520.16 ± 73.16*	7.53 ± 0.47*	6.74 ± 2.20*	4.00 ± 1.27	50.97 ± 3.42*	35.77 ± 4.48
Curcumin	XI without Borneol	719.55 ± 63.13	9.61 ± 0.40	10.09 ± 4.08	5.33 ± 1.63	50.45 ± 5.25	22.27 ± 4.11
	XI	784.78 ± 83.52*	7.33 ± 0.33*	6.57 ± 2.91	2.67 ± 1.03	82.75 ± 5.38*	23.80 ± 3.60
Demethoxycurcumin	XI without Borneol	364.07 ± 37.18	9.27 ± 0.20	14.21 ± 2.57	3.67 ± 0.82	28.03 ± 3.17	38.97 ± 5.00
	XI	467.20 ± 55.74*	7.63 ± 0.34*	7.01 ± 1.83*	3.00 ± 1.10	46.51 ± 4.02*	39.57 ± 6.97
Bisdemethoxycurcumin	XI without Borneol	449.78 ± 48.41	8.01 ± 0.28	9.50 ± 3.09	2.67 ± 1.03	47.53 ± 6.65	38.15 ± 7.50
	XI	569.40 ± 68.43*	6.60 ± 0.33*	5.37 ± 1.59*	2.33 ± 0.82	67.05 ± 5.01*	33.87 ± 4.78

* $P < 0.05$ *vs* oral administration of Xintiantai I without borneol.

2013). Borneol has definite effects on promotion of bioactive components' AUC, T_{max}, and C_{max} during the coadministration with it.

According to some literature (Lai et al., 2011; Wang et al., 2009), borneol implied a slower distribution and elimination with longer $t_{1/2}$ and MRT of analytes when coadministered. In our research, we found that borneol speeded up the remover and shortened the residence of bioactive components with a shorter MRT and $t_{1/2z}$ to the contrary. It may be because of P450-mediated drug-drug interaction when coadministered. Cytochromes P450 are the major drug-metabolizing enzymes because they are responsible for 70%–80% of all phase I dependent metabolism of clinically useful drugs. Borneol can increase the hepatic CYP2D, CYP2B1/2 and CYP3A expression at the mRNA and protein levels, and activity to accelerate the metabolism of coadministered drugs (Chen, Huang, Wang, & Chen, 2017,; 2015; Zhang, Mi, & Wang, 2013). When drugs were coadministered with borneol, a certain P450 isoforms were activated thus increased the drugs metabolism.

5. Conclusion

A UHPLC-MS/MS method was employed for the determination of 17 bioactive components (ginsenoside Rg1, Rb1, Rd, berberine, epiberberine, jatrorrhizine, palmatine, columbamine, coptisine, evodiamine, dehydroevodiamine, rutaecarpine, limonin, hyperin, curcumin, demethoxycurcumin and bisdemethoxycurcumin) in rats plasma after oral administration of Xintiantai I, and was successfully applied to the comparison of pharmacokinetic behaviors after dosing with Xintiantai I and Xintiantai I without borneol. In comparative pharmacokinetic studies, the experimental results demonstrated that the borneol could promote the absorption of G-Rd, palmatine, hyperin, curcumin, demethoxycurcumin, and bisdemethoxycurcumin and the clearance of epiberberine, coptisine, and rutaecarpine. This study provided valuable pharmacokinetics information of Xintiantai I for three times a day dosage regimen in clinic and beneficial clinical compatibility of traditional Chinese medicine.

Declaration of Competing Interest

The authors declare no conflict of interests.

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