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Pharmacokinetics of Anthraquinones in Xiexin Decoction and in Different Combinations of its Constituent Herbs

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Xiexin decoction (XXD), a classic pyretolysis formula, is composed of *Rhei Rhizoma* (DH), *Radix Scutellaria* (HQ) and *Coptis Chinensis* (HL) and is commonly used in the clinical setting. The aim of this study was to investigate the pharmacokinetic differences of the five anthraquinones in rats after oral administration of XXD and different combinations of its constituent herbs. Twenty rats were randomly divided into four groups and were administered one of the four extracts: DH, DH-HQ, DH-HL and XXD (DH-HQ-HL) via intragastric gavage. Anthraquinone concentrations in plasma were determined by an HPLC technique. Pharmacokinetic parameters were calculated from the plasma concentration–time data. Compared with DH alone, the DH-HL combination decreased C_{max} of all five anthraquinones and *AUC* of four anthraquinones (except physcion), and the DH-HQ combination decreased *AUC* of aloe-emodin and C_{max} of rhein. Finally, XXD increased *AUC* of all five anthraquinones compared with DH-HL combination. These results showed that the oral bioavailabilities of five anthraquinones were decreased significantly by combining DH with HL, whereas HQ weakened the effect of HL that inhibited the absorption of anthraquinones. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Xiexin decoction; compatibility; anthraquinone; pharmacokinetics; rats.

INTRODUCTION

Most Chinese medicinal herbs are prescribed in combinations that are aimed either to produce synergistic effects or to diminish adverse reactions. Pharmacokinetic studies have been proved useful in elucidating the rationale of traditional Chinese medicine (TCM) compatibility. For example, the C_{max} and *AUC* of wogonoside were increased after oral administration of Huangqin-Tang decoction compared with the single Huangqin decoction (Zuo *et al.*, 2003). The bioavailability of ephedrine was increased after combination of *Ramulus Cinnamomi*, *Semen Armeniacae Amarum* and *Radix Glycyrrhizae* with *Herba Ephedrae* (He and Luo, 2005). On the other hand, there were also some reports of the negative influence of TCM compatibility on pharmacokinetics of active components in formula, for example, Shuang–Huang–Lian reduced the bioavailability of baicalein (Di *et al.*, 2006) and components of the other herbs used in Longdan Xiegan Tang had a significant inhibitory effect on gentiopicroside absorption (Wang *et al.*, 2007).

Xiexin decoction (XXD), a classic pyretolysis formula from the *Synopsis of Golden Chamber*, is composed of *Rhei Rhizoma* (DH), *Radix Scutellaria* (HQ) and *Coptis Chinensis* (HL). XXD is commonly employed in the clinical setting. Modern pharmacological studies revealed that XXD has a variety of effects. XXD is an antiinflammatory (Ma *et al.*, 2006; Lo *et al.*, 2005), an antimicrobial (Li *et al.*, 2004), an anticoagulant (Liu *et al.*, 2003) and an antihypertensive agent (Sanae *et al.*, 2001) to name only a few. Xue reported that a precipitate was produced during the preparation of XXD (Xue *et al.*, 1999); however, no information regarding the pharmacokinetic comparisons of XXD with various combinations of its constituent herbs appears to be available.

The anthraquinone components of *Rhei Rhizoma* in XXD, mainly including aloe-emodin, rhein, emodin, chrysophanol and physcion (Fig. 1), have a variety of reported pharmacological activities. These include: inhibiting the production of nitric oxide (NO) and malondialdehyde (MDA) induced by lipopolysaccharide (Wang *et al.*, 2002; Zhang *et al.*, 2004), an antibacterial action (Subhalakshmi *et al.*, 2005), hepatoprotection (Guo *et al.*, 2002; Meng *et al.*, 2005) and others. Therefore, these anthraquinone components are considered to be the active components of *Rhei Rhizoma* in XXD. Given this information, the purpose of this study was to determine the pharmacokinetic differences of the anthraquinone components in rats after oral administration of XXD and the different combinations of its constituent herbs.

MATERIALS AND METHODS

Chemicals. Anthraquinone standards (aloe-emodin, rhein, emodin, chrysophanol and physcion) were purchased from the National Institute for the Control of

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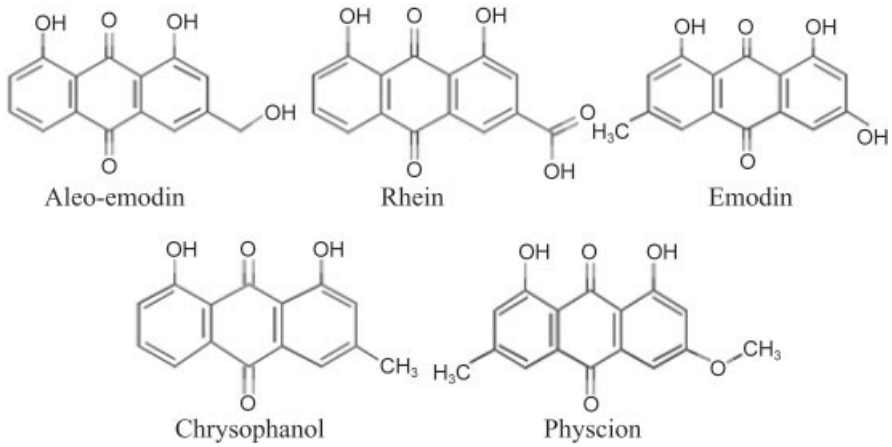

Figure 1. The chemical structure of anthraquinones.

Pharmaceutical and Biological Products (Beijing, China). 1,8-Dihydroxyanthraquinone (internal standard, IS), HPLC-grade methanol and ether were obtained from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China). HPLC-grade water from Milli-Q system (Millipore, Bedford, MA, USA) was used. All other chemicals were of analytical grade. DH, HL and HQ were purchased from Kang Qiao Chinese Cut Crude Drug Co. Ltd (Shanghai, China) and were authenticated by Professor Zhao (Department of Pharmacognosy, Shanghai University of TCM).

Drug preparation. To prepare the XXD, all three crude drugs (DH, HL and HQ) were mixed together in a ratio of 2:1:1 and macerated in deionized water for 30 min. A ten-fold mass of water was added and the mixture was decocted for 1.5 h, and then filtered. An eight-fold mass of water was subsequently added and the mixture was decocted for an additional hour. The filtrates from each decoction were combined and evaporated to dryness under reduced pressure at 60 °C. The same procedure was repeated for the following combinations: DH-HL, HQ-DH and DH. The anthraquinone contents of each combination were determined by high-performance liquid chromatography (HPLC) analysis (Shi *et al.*, 2007).

Animals. Sprague-Dawley rats, weighing 276 ± 20 g (Certificate No. SYXK 2004-2005) were provided by the Animal Center of Shanghai University of Traditional Chinese Medicine. They were maintained on a 12 h light–dark cycle in an environmentally controlled breeding room (temperature 22–25 °C, humidity 60% ± 5%) for 7 days. The animals were fasted for 12 h prior to experimentation, but continued to have free access to water during this time. The animal experiments were conducted in accordance with the Institute's Guide for the Care and Use of Laboratory Animals.

Determination of anthraquinones in plasma (Yan and Ma, 2007). The integrated HPLC system (Alliance Waters, USA) was equipped with a 2695 separation module, 2487 dual λ absorbance detector, 2475 multi λ fluorescence detector and Empower2 chemstation. Compounds were separated using a Thermo Hypersil-Keystone C_{18} column (5 μm, 250 × 4.6 mm) at 40 °C temperature. The mobile phase was composed of water: phosphoric acid (100:0.1 v/v) and methanol with gradient elution. The flow rate was 1 mL/min. Detection was performed at wavelengths of 435 and 515 nm for excitation and emission, respectively.

Liquid–liquid extraction (LLE) was used for the sample preparation in this investigation. The chromatographic profiles of anthraquinone standards, blank plasma, blank plasma spiked with anthraquinone standards, and plasma sample obtained 0.5 h after oral administration of XXD in the Sprague-Dawley rats are shown in Fig. 2.

Assay validation. Known amounts of anthraquinones and IS were added into 200 μL of blank plasma to prepare the following series of standards: 6.5–1300 ng/mL aloe-emodin, 20–4000 ng/mL rhein, 40–8000 ng/mL emodin, 15–3000 ng/mL chrysophanol and 13–2600 ng/mL physcion. All five anthraquinone standard sets had good linearity with their own linearity range. The quality control (QC) samples were prepared at three different concentrations (13, 130 and 1300 ng/mL for aloe-emodin, 40, 400 and 4000 ng/mL for rhein, 80, 800 and 8000 ng/mL for emodin, 30, 300 and 3000 ng/mL for chrysophanol and 26, 260 and 2600 ng/mL for physcion). Validation was performed by establishing the within-batch and between-batch accuracy, precision, recovery and stability of the method on quality control (QC) samples.

The extraction recoveries of the anthraquinones were 62.4–89.9%. The within-batch accuracy of anthraquinones was 95.2–104.4% with a coefficient of variation (CV) values of <5.5%. The between-batch accuracy of anthraquinones was 90.3–108.8% with CV values of <13.4%. The results of the stability test showed that accuracy of aloe-emodin, rhein, emodin, chrysophanol and physcion was 92.1–112.7 % with CV values of <11.7%, under all conditions indicating that the samples were stable throughout the testing process.

Pharmacokinetic study. Twenty rats were randomly divided into four groups. Each group received a single intragastric gavage (i.g.) administration of XXD, DH-HQ, DH-HL or DH. The dose of XXD was 12 g/kg body weight. This dose was the same as the effective dose used in rats (Wu *et al.*, 2003) and twice the effective dose used in humans (Ren, 1996). The dose of DH-HQ, DH-HL and DH was the same as the amount of crude drug DH in XXD. All doses are shown in Table 1.

All extractions were prepared as aqueous solutions. A blood sample was drawn into a heparinized tube immediately prior to i.g. administration, and at 0.083,

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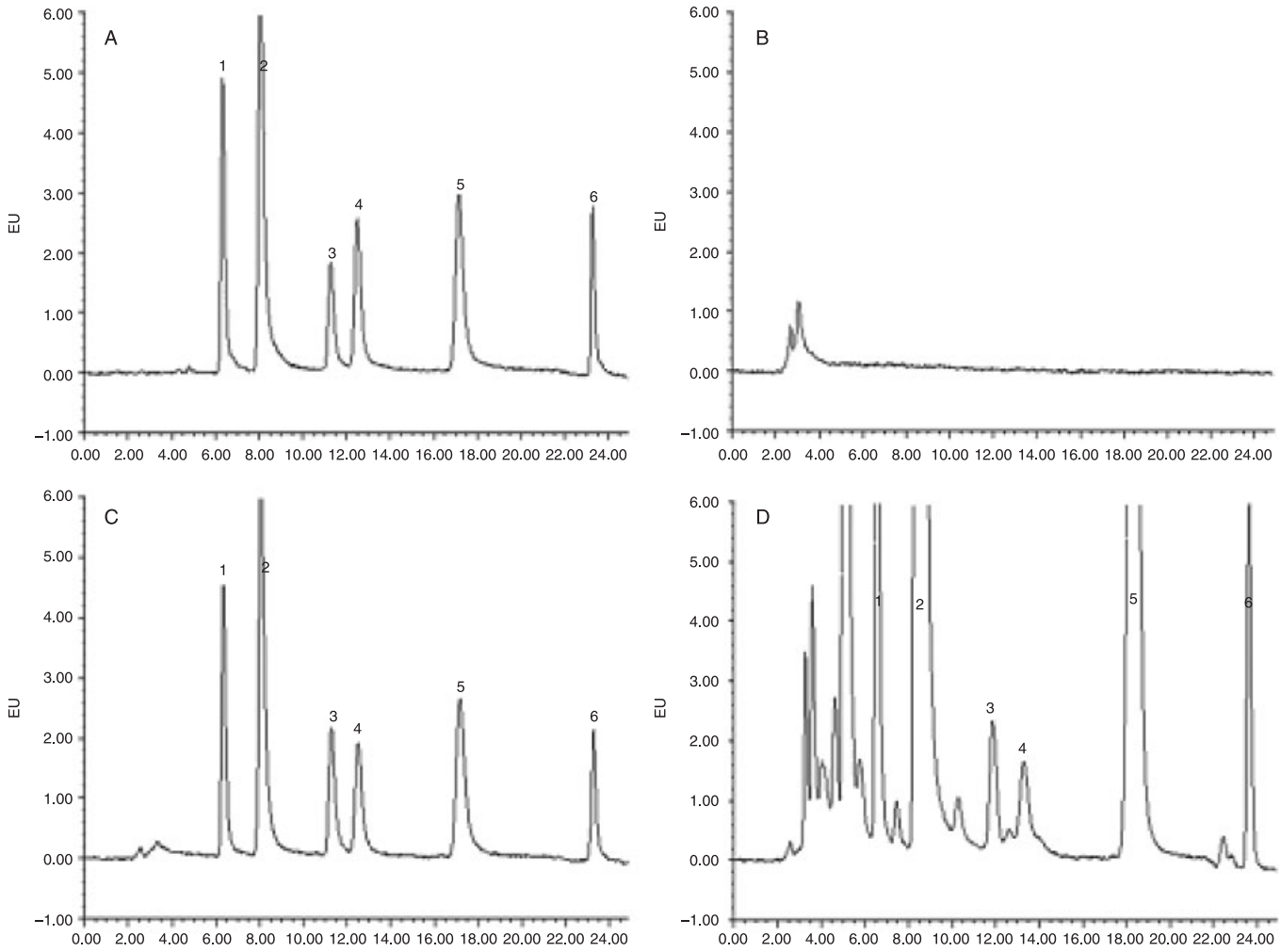

Figure 2. Chromatograms of anthraquinones. (A) Standards and IS; (B) Blank plasma; (C) Blank plasma spiked with standards and IS; (D) Plasma sample after i.g. administration of XXD. 1, aloe-emodin; 2, rhein; 3, IS; 4, emodin; 5, chrysophanol; 6, physcion.

Table 1. Doses of four extracts given in four treatment groups

Group	DH (g/kg)	HQ (g/kg)	HL (g/kg)	Aloe-emodin (mg/kg)	Rhein (mg/kg)	Emodin (mg/kg)	Chrysophanol (mg/kg)	Physcion (mg/kg)
XXD	6	3	3	2.68	10.38	3.32	2.75	0.78
DH-HQ	6	3	–	4.29	13.43	6.21	4.33	1.06
DH-HL	6	–	3	3.00	6.44	3.59	2.13	0.46
DH	6	–	–	2.74	11.01	3.03	1.88	0.59

0.25, 0.5, 1, 2, 4, 6, 10, 14, 24, 36 and 48 h post-i.g. administration. The plasma was isolated and maintained at –70 °C until time of analysis. Plasma concentrations of anthraquinones were measured as described above. Samples that were found to contain concentrations above the higher limit of quantification were diluted with blank plasma and then re-analysed.

Pharmacokinetic analysis. The plasma concentrations of anthraquinones were evaluated using the equation from the standard curves that were run with each batch of samples. The plasma concentration–time data were analysed with the Drug and Statistics 2.0 software package to determine pharmacokinetic parameters. The observed value of C_{max} was obtained from the observed data and the observed value of AUC_{0-t} was calculated using the trapezoidal rule. The dose-normalized values of C_{max} and AUC_{0-t}, C_{max}/dose and AUC_{0-t} /dose, were calculated by dividing the observed values of C_{max} and AUC_{0-t} by the dose of anthraquinones in each extract. The total AUC of five anthraquinones was calculated by summing each AUC value of the five anthraquinones.

Statistical analysis. The results were expressed as mean ± SD. The differences of pharmacokinetic parameters among four groups were tested by one-way analysis of variance (ANOVA). Values of $p < 0.05$ were considered statistically significant.

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RESULTS

The mean plasma concentration–time profiles of anthraquinones are shown in Fig. 3 after i.g. administration of XXD 12 g/kg, DH-HQ 9 g/kg, DH-HL 9 g/kg and DH 6 g/kg. In all the combinations, the absorption of anthraquinones was rapid, with peak concentrations occurring at 15–30 min post-i.g. administration. In all of four combinations, the rhein concentration was the highest among of all five anthraquinones. The emodin concentration in plasma was lower than the limit of quantification after 1 h in DH-HL, 2 h in DH and DH-HQ and 4 h in XXD.

The pharmacokinetic parameters of anthraquinones are shown in Tables 2–6. The pharmacokinetic parameters, C_{max} and AUC of all five anthraquinones and $T_{1/2}$ of aloe-emodin, rhein and physcion, were significant different among the four treatment groups ($p < 0.05$ or $p < 0.01$). Among the observed values, C_{max} of all five anthraquinones and AUC of four anthraquinones (except physcion) were lower in the DH-HL group than those in the DH group, AUC of emodin, chrysophanol and physcion were higher in DH-HQ and XXD groups than that in the DH group and total AUC of five anthraquinones was higher in the DH-HQ group than that in the DH group (Fig. 4). Among the dose-normalized values, the DH-HL combination decreased the C_{max} of all five anthraquinones and AUC of four anthraquinones (except physcion), and the DH-HQ combination decreased AUC of aloe-emodin and C_{max} of rhein, compared with the parameters of the anthraquinones in DH. The AUC of all five anthraquinones were higher in the XXD group than those in the DH-HL group, and the AUC of physcion was higher in XXD group than that in the DH group.

DISCUSSION

To date, there have been two reports about the influence of TCM compatibility on the pharmacokinetics of anthraquinones in the formula. The compatibility of the Taohe Chengqi decoction promoted the absorption of rhein (Xie *et al.*, 2005) and rhein from Da-Cheng-Qi decoction was absorbed well with larger AUC in plasma than that from Xiao-Cheng-Qidecoction (Tang *et al.*, 2007). However, the results are not enough to elucidate the influence of TCM compatibility on the pharmacokinetics of multiple anthraquinone components in traditional Chinese decoction containing DH, since only one of the anthraquinones, rhein, was studied. The influence of XXD compatibility on pharmacokinetics of anthraquinones in the formula has not been studied. The results of this study showed that the pharmacokinetic parameters, AUC and C_{max} of five anthraquinones were dramatically different after oral administration of XXD and the different combinations of its constituent herbs. The oral bioavailability of anthraquinones was decreased significantly by combination of DH with HL. Although HQ *per se* had some retarding influence on the absorption of aloe-emodin and rhein, to a larger extent, it weakened the effect of HL that markedly inhibited the absorption of anthraquinones because the dose-normalized AUCs of five anthraquinones were higher in the XXD (DH-HQ-HL) group than those in the DH-HL group.

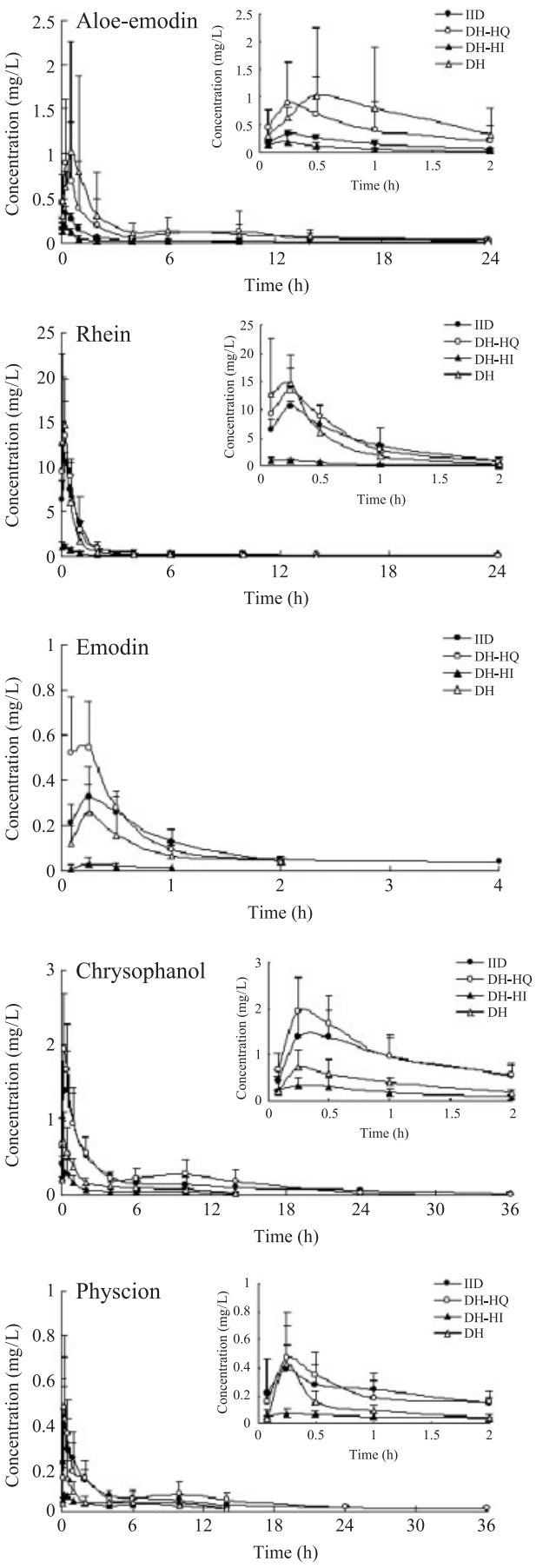

Figure 3. Average plasma concentration–time curves of anthraquinones after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$).

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Table 2. Pharmacokinetic parameters of aloe-emodin after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$)

Parameter	XXD	DH-HQ	DH-HL	DH
$AUC_{(0-t)}$ [(ng/mL)•h][e]	590 ± 298[a]	2425 ± 3452[d]	238 ± 189[b]	2885 ± 3646
$AUC_{(0-t)}$/dose [(ng/mL)•h/(mg/kg)][f]	220 ± 111[c]	566 ± 805[b]	79 ± 63[b]	1052 ± 1329
$T_{1/2}$ (h)	4.9 ± 2.9	7.5 ± 1.6[b,d]	2.2 ± 1.4	3.2 ± 0.7
T_{max} (h)	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.1	0.4 ± 0.1
Cl/F (L/kg/h)	4.8 ± 1.9	3.9 ± 2.3	19.1 ± 14.1	2.0 ± 1.3
Vd/F (L/kg)	28.1 ± 5.8	42.7 ± 26.9	41.2 ± 13.5	8.5 ± 4.8
C_{max} (ng/mL)[e]	349 ± 54[a]	895 ± 728[d]	217 ± 124[b]	1140 ± 1169
C_{max}/dose [(ng/mL)/(mg/kg)][f]	130 ± 20	209 ± 170[c]	72 ± 42[b]	416 ± 426

[a] $p < 0.05$, [b] $p < 0.01$ vs DH; [c] $p < 0.05$, [d] $p < 0.01$ vs DH-HL; [d] observed value, [e] dose-normalized value.

Table 3. Pharmacokinetic parameters of rhein after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$)

Parameter	XXD	DH-HQ	DH-HL	DH
$AUC_{(0-t)}$ [(ng/mL)•h][e]	12657 ± 7768[d]	12376 ± 2816[d]	1575 ± 422[b]	10240 ± 2940
$AUC_{(0-t)}$/dose [(ng/mL)•h/(mg/kg)][f]	1219 ± 748[d]	922 ± 210[d]	245 ± 66[b]	930 ± 267
$T_{1/2}$ (h)	4.0 ± 1.8	5.9 ± 2.4	5.1 ± 0.9[a]	2.9 ± 0.3
T_{max} (h)	0.3 ± 0.1	0.3 ± 0.0	0.2 ± 0.1	0.2 ± 0.1
Cl/F (L/kg/h)	1.0 ± 0.3	1.1 ± 0.3	3.8 ± 0.9	1.1 ± 0.4
Vd/F (L/kg)	5.0 ± 2.0	8.7 ± 2.2	27.6 ± 6.2	4.7 ± 1.2
C_{max} (ng/mL)[e]	11078 ± 1372[a,d]	13352 ± 3978[d]	1205 ± 386[b]	18700 ± 6104
C_{max}/dose [(ng/mL)/(mg/kg)][f]	1067 ± 132[a,d]	994 ± 296[a,d]	187 ± 60[b]	1699 ± 554

[a] $p < 0.05$, [b] $p < 0.01$ vs DH; [c] $p < 0.05$, [d] $p < 0.01$ vs DH-HL; [e] observed value, [f] dose-normalized value.

Table 4. Pharmacokinetic parameters of emodin after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$)

Parameter	XXD	DH-HQ	DH-HL	DH
$AUC_{(0-t)}$ [(ng/mL)•h][e]	319 ± 92[a,d]	377 ± 100[b,d]	25 ± 11[b]	185 ± 89
$AUC_{(0-t)}$/dose [(ng/mL)•h/(mg/kg)][f]	96 ± 28[d]	61 ± 16[d]	7 ± 3[b]	61 ± 29
$T_{1/2}$ (h)	0.5 ± 0.2	0.4 ± 0.1	–	–
T_{max} (h)	0.3 ± 0.0	0.1 ± 0.1	0.3 ± 0.0	0.4 ± 0.1
Cl/F (L/kg/h)	8.1 ± 1.7	17.2 ± 5.8	–	–
Vd/F (L/kg)	7.7 ± 1.5	8.9 ± 2.8	–	–
C_{max} (ng/mL)[e]	341 ± 102[d]	602 ± 193[a,d]	88 ± 31[b]	280 ± 92
C_{max}/dose [(ng/mL)/(mg/kg)][f]	103 ± 31[d]	97 ± 31[d]	25 ± 9[b]	92 ± 30

[a] $p < 0.05$, [b] $p < 0.01$ vs DH; [c] $p < 0.05$, [d] $p < 0.01$ vs DH-HL; [e] observed value, [f] dose-normalized value.

Table 5. Pharmacokinetic parameters of chrysophanol after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$)

Parameter	XXD	DH-HQ	DH-HL	DH
$AUC_{(0-t)}$ [(ng/mL)•h][e]	4864 ± 1868[a,d]	6826 ± 3075[b,d]	1017 ± 552[a]	1952 ± 602
$AUC_{(0-t)}$/dose [(ng/mL)•h/(mg/kg)][f]	1770 ± 680[d]	1576 ± 710[d]	478 ± 259[a]	1037 ± 320
$T_{1/2}$ (h)	7.7 ± 2.6	6.2 ± 1.0	7.0 ± 2.8	5.7 ± 0.7
T_{max} (h)	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
Cl/F (L/kg/h)	0.6 ± 0.3	0.8 ± 0.7	2.4 ± 2.1	0.9 ± 0.3
Vd/F (L/kg)	6.1 ± 2.6	7.7 ± 6.6	19.4 ± 7.7	7.3 ± 2.8
C_{max} (ng/mL)[e]	1488 ± 531[d]	2005 ± 724[a,d]	445 ± 219[b]	887 ± 169
C_{max}/dose [(ng/mL/(mg/kg)][f]	542 ± 193[d]	463 ± 167[d]	209 ± 103[b]	471 ± 90

[a] $p < 0.05$, [b] $p < 0.01$ vs DH; [c] $p < 0.05$, [d] $p < 0.01$ vs DH-HL; [e] observed value, [f] dose-normalized value.

The effects of Xiexin decoction and its constituents (DH, HL, HQ, DH-HL, DH-HQ, HL-HQ) on the serum NO concentration of LPS-challenged mice was performed according to the principle of orthogonal design. The NO concentrations of every group treated with any component of the Xiexin decoction or the combination of two or three of them were lower than that of the model group, and a significant difference was not found only in the HL. Variance analysis showed that as far as the antiinflammatory effect was concerned, DH was the most important component in this decoction, followed by HQ. Variance analysis also showed that synergy was found

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Table 6. Pharmacokinetic parameters of physcion after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$)

Parameter	XXD	DH-HQ	DH-HL	DH
$AUC_{(0-t)}$ [(ng/mL)•h][e]	1282 ± 428[a,d]	1684 ± 767[b,d]	352 ± 264	519 ± 216
$AUC_{(0-t)}$/dose [(ng/mL)•h/(mg/kg)][f]	1640 ± 547[a,c]	1584 ± 721	757 ± 568	882 ± 367
$T_{1/2}$ (h)	6.8 ± 2.7	9.6 ± 3.6[a,c]	4.5 ± 2.5	5.6 ± 1.7
T_{max} (h)	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
Cl/*F* (L/kg/h)	0.6 ± 0.2	0.7 ± 0.3	1.4 ± 0.7	0.9 ± 0.2
*V*d/*F* (L/kg)	5.3 ± 1.7	8.2 ± 3.7	7.9 ± 4.5	7.0 ± 2.9
C_{max} (ng/mL)[e]	401 ± 187[d]	478 ± 226[d]	93 ± 36[b]	395 ± 328
C_{max}/dose [(ng/mL/(mg/kg)][f]	512 ± 240	449 ± 213	200 ± 77[a]	671 ± 558

[a] $p < 0.05$, [b] $p < 0.01$ vs DH; [c] $p < 0.05$, [d] $p < 0.01$ vs DH-HL; [e] observed value, [f] dose-normalized value.

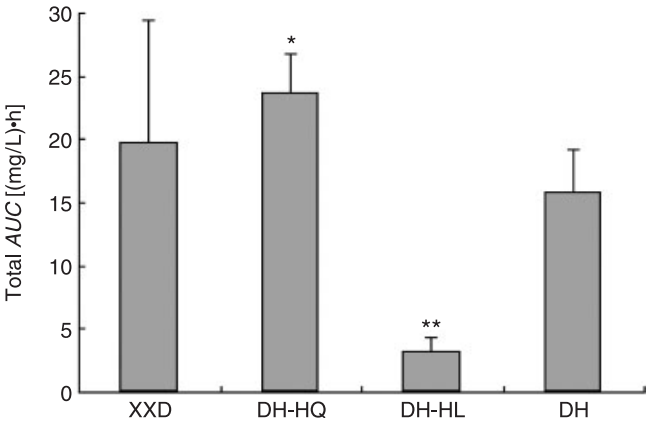

Figure 4. Total *AUC* of five anthraquinones after i.g. administration of XXD, DH-HQ, DH-HL and DH in rats ($\bar{x} \pm s$, $n = 5$). * $p < 0.05$, ** $p < 0.01$ vs DH.

between DH and HQ (Ma *et al.*, 2007). In the present study, the total systemic exposure level of five anthraquinones (total *AUC*) was higher in the DH-HQ group than that in DH group, which can, at least partially, explain the synergism between DH and HQ.

The content of anthraquinones in four extracts were quite different due to the preparation of decoction (Shi *et al.*, 2007). The reason for the decrease of anthraquinones in the DH-HL may be the precipitation caused by conjugation of the anthraquinones in DH with protoberberine alkoloids in HL. The reason for the increase of anthraquinones in DH-HQ is unclear. In pharmacokinetic analyses and statistical analyses, the dose-normalized *AUC* and C_{max} values were calculated so as to avoid the influence of the different contents of anthraquinones in four extracts.

This study indicates that HL decreased the bioavailability of the anthraquinones in XXD, and suggested that it might elicit significant drug–drug interaction when administered in combination with drugs similar to anthraquinones. While the mechanisms of the pharmacokinetic interaction identified in the study remain unclear, further research in this field is certainly warranted based on the progress made here.

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REFERENCES

Di B, Feng N, Liu W. 2006. Pharmacokinetic comparisons of Shuang-Huang-Lian with the different combinations of its constitutional herbs. *J Ethnopharmacol* **107**: 401–405.

Guo MZ, Li XS, Xu HR, Mei ZC, Shen W, Ye XF. 2002. Rhein inhibits liver fibrosis induced by carbon tetrachloride in rats. *Acta Pharmacol Sin* **23**: 739–744.

He F, Luo JB. 2005. Pharmacokinetic study of minister, adjuvant, and guide herbs in Mahuang Decoction to ephedrine in monarch herb *in vivo*. *Chin Tradit Herb Drugs* **36**: 1313–1316.

Li JR, Zhang GP, Wu LS, Yan MZ, Song HY. 2004. Pharmacodynamic study on the sediments that produced by matching of herbs in Xiexintang. *Chin J Exp Tradit Med Formul* **10**: 27–30.

Liu BL, Xuan YY, Wang XH, Liu XH. 2003. Pharmacodynamic study of Sanhuang Xiexin Tang for treatment of upper gastrointestinal hemorrhage. *Pharmacol Clin Chin Mater Med* **19**: 1–3.

Lo YC, Tsai PL, Huang YB *et al.* 2005. San-Huang-Xie-Xin-Tang reduces lipopolysaccharides-induced hypotension and inflammatory mediators. *J Ethnopharmacol* **96**: 99–106.

Ma BL, Ma YM, Yan DM, Wang TM, Shi R, Tan B. 2007. Comparative study on anti-inflammatory effects of Xiexin decoction and its constituents. *Chin Tradit Herb Drugs* **38**: 1690–1693.

Ma YM, Yan JC, Wang TM, Shi R, Jiao YB. 2006. Anti-inflammatory effects of Xiexin decoction on animal models of acute inflammation. *Chin Pharmacol Bull* **22**: 1393–1398.

Meng KW, Lv Y, Yu L, Wu SL, Pan CE. 2005. Effects of emodin and double blood supplies on liver regeneration of reduced size graft liver in rat model. *World J Gastroenterol* **11**: 2941–2944.

Ren J. 1996. Synopsis of golden chamber. In *Zhongguolidaimingyimingfangquanshu*, Ren J (ed.). Academy Press: Beijing, 35.

Sanae F, Komatsu Y, Chisaki K, Kido T, Ishige A, Hayashi H. 2001. Effects of San'o-shasin-to and the constituent herbal medicines on theophylline-induced increase in arterial blood pressure of rats. *Biol Pharm Bull* **24**: 1137–1141.

Shi R, Ma YM, Ye FY, Zhang N, Wang TM. 2007. Study on the quantitative change of five anthraquinones in Xiexin decoction of different combinations. *Chin Tradit Herb Drugs* **38**: 1327–1330.

Subhalakshmi B, Abhijit G, Banasri H. 2005. Evaluation of the antibacterial activity of *Ventilago madraspatana* Gaertn., *Rubia cordifolia* Linn. and *Lantana camara* Linn.: isolation of emodin and physcion as active antibacterial agents. *Phytother Res* **19**: 888–894.

Tang WF, Huang X, Yu Q *et al.* 2007. Determination and

pharmacokinetic comparison of rhein in rats after oral dosed with Da-Cheng-Qi Decoction and Xiao-Cheng-Qi decoction. *Biomed Chromatogr* **21**: 1186–1190.

Wang CC, Huang YJ, Chen LG, Lee LT, Yang LL. 2002. Inducible nitric oxide synthase inhibitors of Chinese herbs III. *Rheum palmatum*. *Planta Med* **68**: 869–874.

Wang CH, Cheng XM, Bligh SW, White KN, Branford-White CJ, Wang ZT. 2007. Pharmacokinetics and bioavailability of gentiopicroside from decoctions of Gentianae and Longdan Xiegan Tang after oral administration in rats – comparison with gentiopicroside alone. *J Pharm Biomed Anal* **44**: 1113–1117.

Wu ZC, Wu K, Wang H, Wang J. 2003. Experimental study on anti-atherosclerosis of Xiexin decoction in rats. *Chin J Gerontol* **23**: 461–471.

Xie H, Ma YM, Wang TM, Ye FY. 2005. Pharmacokinetics of rhein in Taohe Chengqi Decoction and rhubarb in rabbits. *Pharmacol Clin Chin Mater Med* **21**: 1–3.

Xue Y, Zhou TH, Wang XM. 1999. Studies on precipitate produced in preparation of complex prescription of Chinese medicines Xiexin Decoction by LC/MS/MS and RP-HPLC. *Chin J Pharm Anal* **19**: 224–228.

Yan DM, Ma YM. 2007. Simultaneous quantification of five anthraquinones in rat plasma by high-performance liquid chromatography with fluorescence detection. *Biomed Chromatogr* **21**: 502–507.

Zhang YQ, Liu ZH, Hu HF. 2004. Effects of rhubarb on nitric oxide and malondialdehyde in mice with endotoxemia. *Chin J TCM WM Crit Care* **11**: 123–125.

Zuo F, Zhou ZM, Zhang Q *et al.* 2003. Pharmacokinetic study on the multi-constituents of Huangqin-Tang decoction in rats. *Biol Pharm Bull* **26**: 911–919.