

# *In vivo* pharmacokinetic comparisons of ferulic acid and puerarin after oral administration of monomer, medicinal substance aqueous extract and Nao-De-Sheng to rats

Zhen Ouyang, Ming Zhao, Jianming Tang, Lulin Pan

School of Pharmacy, Pharmacognosy Jiangsu University, Zhenjiang, 212013, PR China

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## ABSTRACT

**Background:** Nao-De-Sheng decoction (NDS), a traditional Chinese medicine (TCM) prescription containing *Radix puerariae lobatae*, *Floscarthami*, *Radix et Rhizoma Notoginseng*, *Rhizoma chuanxiong* and *Fructus crataegi*, is effective in the treatment of cerebral arteriosclerosis, ischemic cerebral stroke and apoplexy linger effect. Ferulic acid and puerarin are the main absorbed effective ingredients of NDS. **Objective:** To assess the affection of other components in medical material and compound recipe compatibility on the pharmacokinetics of ferulic acid and puerarin, of ferulic acid from the monomer *Rhizoma chuanxiong* aqueous extract and NDS were studied. And pharmacokinetics comparisons of puerarin from the monomer *Radix puerariae* extract and NDS decoction were investigated simultaneously. **Materials and Methods:** At respective different time points after oral administration of the monomer, medicinal substance aqueous extract and NDS at the same dose in rats, plasma concentrations of ferulic acid and puerarin in rats were determined by RP-HPLC, and the main pharmacokinetic parameters were estimated with 3P97 software. **Results:** The plasma concentration-time curves of ferulic acid and puerarin were both best fitted with a two-compartment model.  $AUC_{0-t}$ ,  $AUC_{0\rightarrow\infty}$ ,  $T_{max}$ , and  $C_{max}$  of ferulic acid in the monomer and NDS decoction were increased significantly ( $P < 0.05$ ) compared with that in *Rhizoma chuanxiong* aqueous extract. And statistically significant increase ( $P < 0.05$ ) in pharmacokinetic parameters of puerarin including  $AUC_{0-t}$ ,  $AUC_{0\rightarrow\infty}$ , CL,  $T_{max}$  and  $C_{max}$  were obtained after oral administration of puerarin monomer compared with *Radix puerariae* extract. Although the changes of  $AUC_{0-t}$ ,  $AUC_{0\rightarrow\infty}$  and CL had no statistically significant,  $C_{max}$  of puerarin in NDS was increased remarkably ( $P < 0.05$ ) compared with that in single puerarin. **Conclusions:** Some ingredients of *Rhizoma chuanxiong* and *Radix puerariae* may be suggested to remarkably influence plasma concentrations of ferulic acid and puerarin. Some ingredients in NDS may increase dissolution and absorption of ferulic acid and puerarin, delay elimination, and subsequently enhance bioavailability of ferulic acid and puerarin in rats after compatibility.

**Key words:** Ferulic acid, medicinal substance aqueous extract, Nao-De-Sheng, pharmacokinetics comparisons, puerarin

## INTRODUCTION

Most herbal medicines are prescribed in combination based on the theory of traditional Chinese medicine (TCM) to obtain synergistic effects or diminish the possible adverse effects. Pharmacokinetic study is useful to explain and predict a variety of events related to the effect and toxicity

of drugs. Thus, it is valuable to perform pharmacokinetic study for evaluating the rationality and compatibility of herbs or prescriptions. Because of the complexity of chemicals in prescriptions, a major activity ingredient is always selected as an indicative compound and the interactions of ingredients in herbs or prescription are clarified based on the pharmacokinetic behavior of the selected compound.<sup>[1,2]</sup>

Nao-De-Sheng decoction (NDS), a traditional Chinese formula containing *Radix puerariae lobatae*, *Floscarthami*, *Radix et Rhizoma Notoginseng*, *Rhizoma chuanxiong* and *Fructus crataegi*, is officially recorded in Chinese Pharmacopoeia<sup>[3]</sup> to be effective in the treatment of cerebral arteriosclerosis,

### Address for correspondence:

Prof. Zhen Ouyang, School of Pharmacy, Jiangsu University, Zhenjiang 212013, PR China.  
E-mail: zhenouyang@ujs.edu.cn

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ischemic cerebral stroke and apoplexy linger effect.<sup>14</sup> *Rhizoma chuanxiong*, a principal agent of NDS, has been used for activating blood circulation to dissipate blood stasis and deoxygenation meridian. Ferulic acid is usually considered as the main pharmacological effective compound with anti-atherosclerosis and anti-platelet agglutination. *Radix puerariae lobatae* is another principal agent of NDS decoction, and puerarin is its main active component. Puerarin has been shown to have beneficial effects on cardiovascular, neurological and hyperglycemic disorders.<sup>15-71</sup>

Pharmacokinetic studies on *Rhizoma chuanxiong* and its active components,<sup>8-10</sup> *Radix puerariae lobatae* and puerarin<sup>11</sup> have been carried out. However, up to now, the pharmacokinetic influence of other herbal medicines in NDS and other composition in single herb extract on ferulic acid and puerarin is seldom reported. The aim of this research is to explore whether there are some herbal ingredients in single herb and complex prescription effecting the pharmacokinetic behavior of ferulic acid and puerarin. It is expected that the results of this study would be helpful for improving clinical therapeutic effect and further pharmacological studies of ferulic acid and puerarin.

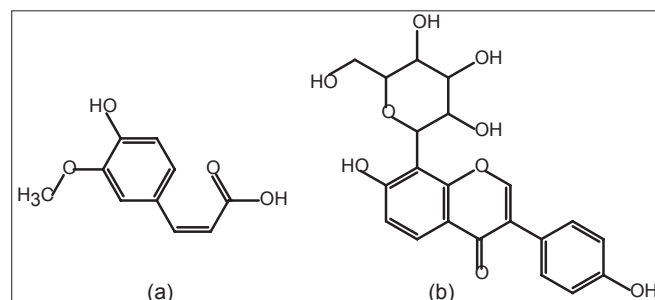
## MATERIALS AND METHODS

### Materials and reagents

*Rhizoma chuanxiong* and *Radix puerariae lobatae* were bought from TongDeTang (The licence No. was SU Y20060352), and authenticated by Dr. OuYang Zhen (Department of Pharmacognosy, Jiangsu University). Ferulic acid and puerarin [Figure 1] were purchased from the NICPBP (National Institute for the Control of Pharmaceutical and Biological Products, China). NDS (The batch No. is 110773-200611) was produced by HuaYu pharmaceuticals company in Harbin. Redistilled water was produced by RO-MB-10D high-purity water machine. Methanol (Han bang, China) was of HPLC grade. Other reagent were commercially available and of analytical grade.

### Liquid chromatographic condition

The HPLC system (LC-1500, JASCO, JAPAN) consisted



**Figure 1:** Chemical structures of ferulic acid (a) and puerarin (b)

of a pump (PU-1580 HPLC pump, JASCO, JAPAN), and a UV detector (UV-1575 Spectrometer, JASCO, JAPAN).

The liquid chromatographic separation of ferulic acid were achieved using on a  $C_{18}$  column (250 mm  $\times$  4.6 mm, 5  $\mu$ m, Kromasil, HanBang, CHINA) with methanol (A) and water (0.5% acetic acid, B) as mobile phase (30:70, V/V) at a rate of 1 mL/min and the UV detection wavelength was at 320 nm and column temperature was 35°C.

The liquid chromatographic separation of puerarin were achieved using on a  $C_{18}$  column (250 mm  $\times$  4.6 mm, 5  $\mu$ m, Kromasil, HanBang, CHINA) with methanol (A) and water (0.5% acetic acid, B) as mobile phase (25:75, V/V) at a rate of 1 mL/min and the UV detection wavelength was at 250nm and column temperature was 30°C.

### Preparation of rhizome chuanxiong and radix puerariae aqueous extract

The dried powder of *Rhizoma chuanxiong* aqueous extract was prepared under the same condition for preparation of NDS that *Rhizoma chuanxiong* cut into slices, and decocted with water two times (1: 14 and 1: 12, w/v, 2 hours each time), then the extraction was lyophilized to powder. The dried powder of *Rhizoma chuanxiong* aqueous extract was kept in 4°C for further oral administration to rats. The content of ferulic acid in the dried powder of *Rhizoma chuanxiong* aqueous extract and NDS decoction were determined by HPLC as 8.26 mg/g and 0.85 mg/g.

The dried powder of *Radix puerariae* aqueous extract was prepared following the extraction conditions of NDS that *Radix puerariae* were crushed to pieces, and decocted with water two times (1.5h and 1h for each time), then the extraction was lyophilized to powder. The content of puerarin in the dried powder of *Radix puerariae* aqueous extract and NDS decoction were determined by HPLC as 122.675 mg/g and 52.67 mg/g.

### Animals

Male Sprague-Dawley (SD) rats, weighing 300-340 g, were bought from the Laboratory Animal Service Center of the JiangSu University. The rats were maintained in an air-conditioned animal quarter at a temperature of  $22 \pm 2$  °C and a relative humidity of  $50 \pm 10$  %. Water and food were allowed ad libitum. The animals were acclimatized to the facilities for five days, and then fasted with free access to water for 18 hours prior to each experiment.

### *In vivo* pharmacokinetic study of ferulic acid and puerarin

#### Drug administration and blood sampling

The SD rats were divided randomly into three groups (each 6 rats), and each group was single administered monomer

group (ferulic acid or puerarin), single herb extract group (*Rhizoma chuanxiong* or *Radix puerariae*) and NDS group, respectively, and the dosage of the monomer, single herb extract and NDS was respectively 14.75 mg/kg and 100 mg/kg. Blood samples of 400  $\mu$ L were collected in heparinized eppendorf tube via the oculi chorioideae vein subsequently at different time points (ferulic acid: 0.083, 0.167, 0.333, 0.5, 1, 1.5, 2, 3, 4, 5 and 6h; puerarin: 0.083, 0.167, 0.25, 0.333, 0.5, 0.667, 1, 2, 3, 4, 5, 6, 7 and 14h) following oral administration. After centrifuging at 10000 rpm for 10 min, the plasma sample were obtained and frozen at -20 °C until analysis.

#### Preparation of plasma sample

Then rat plasma samples (100  $\mu$ L) were spiked with 200  $\mu$ L methanol by vortex mixing for 2 min. The mixture was then centrifuged at 10,000 rpm for 10 min at room temperature to separate the precipitated protein. An aliquot of 200  $\mu$ L supernatant was transferred to a fresh tube and for each time 20  $\mu$ L was injected into JASCO LC-1500 HPLC system. Then, the concentration of ferulic acid and puerarin was determined.

#### Method validation

##### Specificity

200  $\mu$ L samples of blank rat plasma and its mixture with analyte, and 200  $\mu$ L of plasma sample after administration of herb extract or NDS were chromatographed to determine which endogenous plasma components contribute to interfere the analyte.

##### Calibration Curve

The standard curve in the plasma of ferulic acid was linear in the range from 50 to 1000 ng/mL and the puerarin was linear in the range from 10 to 1000 ng/mL.

##### Recovery

The recoveries of ferulic acid and puerarin were calculated by comparing chromatographic peak areas from unextracted standard samples and from extracted standard samples at three quality control levels (high, medium and low) ( $n = 6$ ), respectively.

##### Precision

The precision of the method were assessed by determination of quality control samples ( $n = 6$ ) on three different validation days. To determine intra-day precision, the assays were carried out on standard solutions of analyte at different times during the same day. Inter-day precision was determined by assaying the standard solutions of analyte over three consecutive days. The concentration of each sample was determined using a calibration curve prepared on the same day.

#### Data analyses

The pharmacokinetic parameter calculations were carried out using the pharmacokinetic software package of 3P97 edited by the Mathematics Pharmacological Committee, Chinese Pharmacological Society. The plasma concentrations at different times were expressed as mean  $\pm$  standard deviation (S.D.) and the mean concentration–time curve was plotted. Statistically significant differences in the pharmacokinetic parameters among different treatment groups were assessed by SAS System for Windows Version 8.2 (SAS Institute, Cary, NC, USA).

## RESULTS

#### Method validation

##### Specificity

Figures 2-3 shows that no interference peaks from endogenous constituents were detected, respectively.

##### Linearity of calibration curve and lower limit of determination

The calibration curves were linear in the determined concentration ranges. And the detection limited for analyses in the range 50 – 1000  $\mu$ g/L for ferulic acid with a correlation coefficient at 0.9994, and 10 – 1000  $\mu$ g/L for puerarin with a correlation coefficient at 0.9993. The mean standard curves were typically described by the equations:  $Y = 127298 X - 4922.3$  for ferulic acid and  $Y = 67.993 X + 1449$  for puerarin. The lower limit of determination was 13  $\mu$ g/L for ferulic acid and 6  $\mu$ g/L for puerarin.

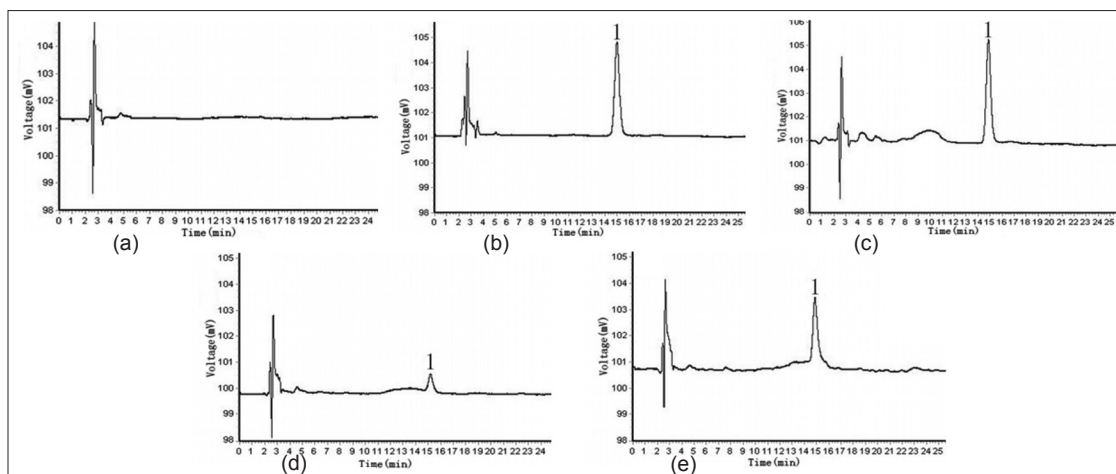
##### Recovery and precision

The recoveries of ferulic acid at each quality control level (100, 500, 1000 $\mu$ g/L) were (97.2  $\pm$  2.0)%, (95.4  $\pm$  2.4)% and (98.8  $\pm$  1.1)%, respectively. The recovery of puerarin at each quality control level (100, 200, 400  $\mu$ g/L) were (90.0  $\pm$  1.0)%, (95.5  $\pm$  1.5)%, (89.8.0  $\pm$  1.8)%, respectively. The extraction recoveries determined for ferulic acid and puerarin were consistent and reproducible.

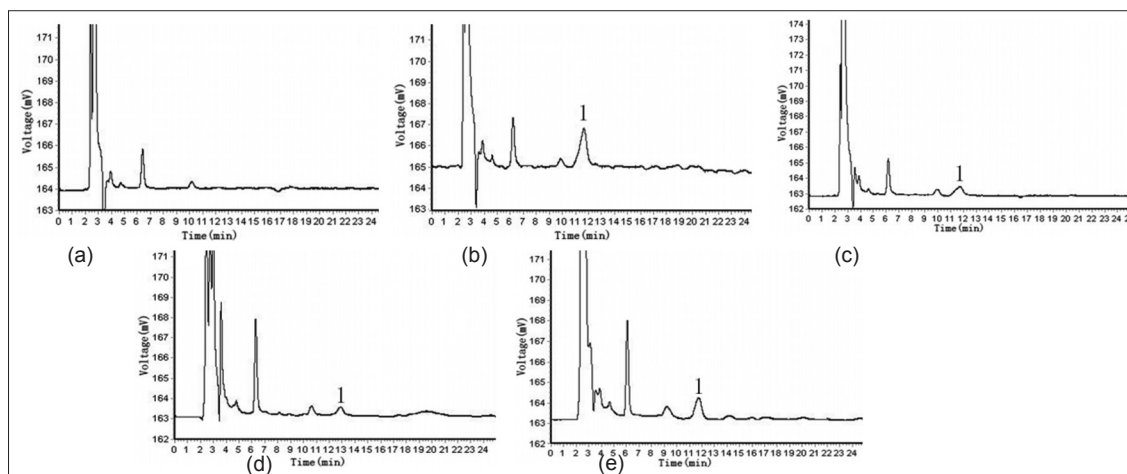
The precision data for ferulic acid and puerarin were given in Table 1, respectively. All values of precision were within recommended limits by chemicals clinical pharmacokinetics technical guidelines.<sup>[12]</sup>

#### Pharmacokinetics study

Plasma concentrations of ferulic acid and puerarin were determined after oral administration of monomer, medicinal substance aqueous extract, and NDS decoction to rats [Figures 2 and 3]. The pharmacokinetic parameters were given in Table 2 and 3, respectively. As shown in Figures 4 and 5, Tables 2 and 3, there were significant differences of  $C_{max}$ ,  $AUC_{0 \rightarrow t}$ , and CL among three groups of ferulic acid and significant differences of  $t_{1/2\alpha}$ ,  $t_{1/2\beta}$



**Figure 2:** The representative HPLC chromatograms of ferulic acid in rat plasma. (a) blank plasma; (b) blank plasma sample spiked with ferulic acid; (c) plasma sample obtained 30min after oral administration of pure ferulic acid at dose of 14.75 mg/kg; (d) plasma sample obtained 30min after oral administration of ferulic acid at dose of 14.75 mg/kg from *Rhizoma chuanxiong* aqueous extract; (f) plasma sample obtained 30min after oral administration of ferulic acid at dose of 14.75 mg/kg from NDS. (1: ferulic acid)



**Figure 3:** The representative HPLC chromatograms of puerarin in rat plasma. (a) blank plasma; (b) blank plasma sample spiked with puerarin; (c) plasma sample obtained 60min after oral administration of pure puerarin at dose of 100 mg/kg; (d) plasma sample obtained 60min after oral administration of puerarin at dose of 100 mg/kg from *Radix puerariae* aqueous extract; (e) plasma sample obtained 60min after oral administration of puerarin at dose of 100 mg/kg from NDS. (1: puerarin)

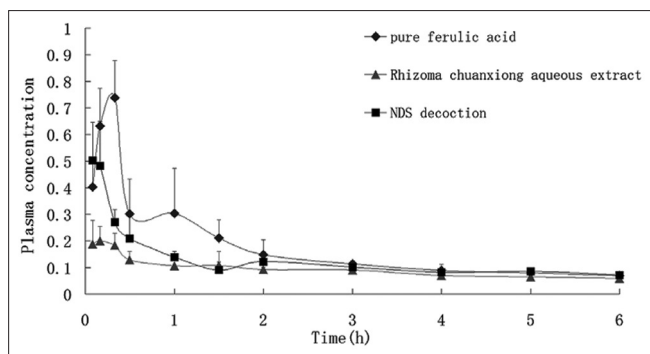
$AUC_{0 \rightarrow \infty}$ ,  $AUC_{0 \rightarrow 24}$ ,  $CL$ ,  $T_{max}$ ,  $C_{max}$  among the three groups of puerarin.

## DISCUSSION

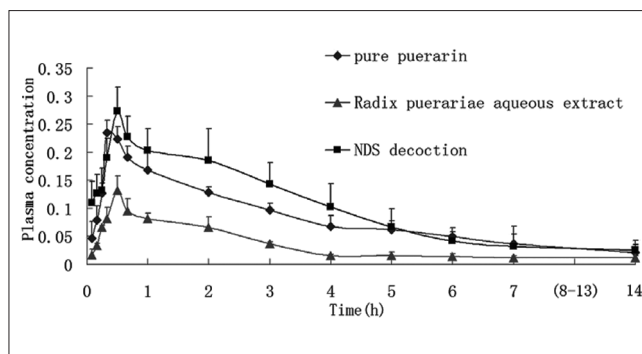
Because of the complexity of chemicals and unknown effective ingredients in prescriptions, pharmacokinetic studies of TCM are faced with many difficulties. Most of the published reports select one or several representative compounds as the targets to investigate the pharmacokinetics of the whole prescription<sup>[13-17]</sup> and elucidate the mechanism of compatibility of compound recipe through pharmacokinetic processes. Several papers focus on how the individual components in the compound prescription interact with other ingredients.<sup>[18-21]</sup> In the

present study, to investigate the pharmacokinetics of ferulic acid and puerarin from monomer, medicinal substance aqueous extract (single herb extract) and NDS (complex prescription), a simple and sensitive RP-HPLC method was developed and validated for pharmacokinetic study of ferulic acid and puerarin. In the present study, protein was precipitated by methanol as pretreatment method to avoid the loss of ingredient absorbed in plasma, and this method was simple and fast and consistent with the requirement of pharmacokinetic study. As shown in Figures 2 and 3, ferulic acid and puerarin could be detected by RP-HPLC system combined with UV detector in rat plasma.

In this study of ferulic acid, the plasma concentration-time curves of ferulic acid were found to be best fitted with a two-compartment model according to 3P97



**Figure 4:** Mean concentration-time profiles of ferulic acid in rats after oral administration of ferulic acid (■), Rhizoma chuanxiong aqueous extract (▲) and NDS decoction (◆). (Each point represents the mean±S.D., n = 6; at a dose containing 14.75 mg/kg ferulic acid)



**Figure 5:** Mean concentration-time profiles of puerarin in rats after oral administration of pure puerarin (■), Radix puerariae aqueous extract (▲) and NDS decoction (◆). (Each point represents the mean±S.D., n = 6; at a dose containing 100 mg/kg puerarin)

**Table 1: Precision and accuracy of ferulic acid and puerarin in rat plasma (n = 6, mean ± S.D.)**

Nominal conc (mg/L)	Intra-day			Inter-day		
	Measured conc (mg/L)	Accuracy (%)	Precision RSD (%)	Measured conc (mg/L)	Accuracy (%)	Precision RSD (%)
<b>Ferulic acid</b>						
0.05	0.054±0.001	108.0	2.0	0.052±0.003	104.0	6.0
0.4	0.422±0.009	105.5	2.3	0.417±0.008	104.3	2.0
1.0	1.027±0.013	102.7	1.3	0.989±0.033	98.9	3.3
<b>Puerarin</b>						
0.04	0.039±0.001	97.5	2.5	0.041±0.001	102.5	2.5
0.1	0.098±0.001	98.0	1.0	0.095±0.005	95.4	5.0
0.4	0.386±0.01	96.5	2.5	0.374±0.007	93.5	1.8

**Table 2: Pharmacokinetic parameters of ferulic acid after oral administration of pure ferulic acid, Rhizoma chuanxiong aqueous extract and NDS decoction in SD rats (at a dose containing 14.75 mg/kg ferulic acid)**

Parameter	Ferulic acid	Ferulic acid from Rhizoma chuanxiong extract	Ferulic acid from NDS decoction
$t_{1/2\alpha}$ (h)	0.164±0.143	0.224±0.029	0.385±0.144
$t_{1/2\beta}$ (h)	3.809±1.047	16.355±4.106**	13.404±3.474***
$AUC_{0 \rightarrow t}$ (μgh/L)	1.023±0.262	0.557±0.050**	0.716±0.051***
$AUC_{0 \rightarrow \infty}$ (μgh/L)	1.108±0.239	0.773±0.063**	1.017±0.103#
CL (L/h/kg)	0.009±0.001	0.025±0.004	0.004±0.003*#
$T_{max}$ (h)	0.180±0.023	0.360±0.062**	0.127±0.046#
$C_{max}$ (μg/L)	0.739±0.140	0.457±0.074**	0.572±0.158***

n=6, mean±S.D.; vs oral administration of ferulic acid group, \*P<0.05, \*\*P<0.01; vs oral administration of *lignsticum chuanxiong* aqueous extract group, #P<0.05, ##P<0.01

**Table 3: Pharmacokinetic parameters of puerarin after oral administration of pure puerarin, Radix puerariae extract and NDS decoction in SD rats (at a dose containing 100 mg/kg puerarin)**

Parameter	Puerarin	Puerarin from Radix puerariae extract	Puerarin from NDS decoction
$t_{1/2\alpha}$ (h)	1.163±0.514**	0.416±0.247	1.238±0.122**
$t_{1/2\beta}$ (h)	6.038±3.340*	10.825±1.955	4.047±1.872***
$t_{1/2K_{el}}$ (h)	0.173±0.177**	0.510±0.084	0.298±0.058***
$AUC_{0 \rightarrow t}$ (μg·h/L)	0.972±0.043**	0.314±0.035	0.936±0.127**
$AUC_{0 \rightarrow \infty}$ (μg·h/L)	1.238±0.069**	0.334±0.049	1.012±0.146**
CL (L/h/kg)	0.119±0.067**	0.281±0.132	0.153±0.044**
$T_{max}$ (h)	0.55±0.264*	0.939±0.147	0.903±0.154#
$C_{max}$ (μg/L)	0.208±0.049*	0.123±0.026	0.262±0.083***

n=6, mean±S.D.; vs oral administration of radix puerariae extract group, \*P<0.05, \*\*P<0.01; vs oral administration of puerarin group, #P<0.05

software. T test showed that there were significant difference in  $AUC_{0\rightarrow t}$ ,  $AUC_{0\rightarrow\infty}$ ,  $T_{max}$ , and  $C_{max}$  between the monomer group and the herb extract group ( $P < 0.05$ ). It could be inferred that some other ingredients in the herb extract have a bad impact on the absorption of ferulic acid and subsequently degrade the bioavailability of ferulic acid in rat plasma. However, the differences among the parameters ( $AUC_{0\rightarrow t}$ ,  $AUC_{0\rightarrow\infty}$ ,  $T_{max}$  and  $C_{max}$ ) of ferulic acid were also considered to be significant ( $P < 0.05$ ) between the NDS and the herb extract. Meanwhile, as shown in Figure 4 and Table 2, it could be inferred that NDS could postpone the elimination of ferulic acid, and increase its absorption time *in vivo* comparing with monomer itself. In addition, NDS could increase the plasma concentration of ferulic acid, subsequently enhance its bioavailability compared with *Rhizoma chuanxiong* aqueous extract.

In the study of puerarin, the concentration-time data demonstrated that puerarin was distributed as an opened two-compartment model according to 3P97 software after oral administration of the drugs. The differences of five parameters of puerarin in rat plasma,  $AUC_{0\rightarrow t}$ ,  $AUC_{0\rightarrow\infty}$ , CL,  $T_{max}$ , and  $C_{max}$  were considered to be significant between the monomer and the herb extract ( $P < 0.05$ ), indicating that *Radix puerariae* extract may be the same to *Rhizoma chuanxiong* aqueous extract that some other ingredients in the herb extract may reduce the absorption of puerarin and subsequently degrade the bioavailability of puerarin in rat plasma. Although the change of  $AUC_{0\rightarrow t}$ ,  $AUC_{0\rightarrow\infty}$ , and CL had no statistically significant [Table 3], the parameter of  $C_{max}$  between pure puerarin group and NDS group was increased remarkably ( $P < 0.05$ ) [Figure 5, Table 3], indicating that NDS could promote the absorption of puerarin, increase the plasma concentration of puerarin, and subsequently enhance the bioavailability in rat plasma.

These results indicated that the pharmacokinetic process of ferulic acid and puerarin in NDS were different from the single herb extract and the monomer in rats: the  $T_{max}$  stepped down and  $AUC_{0\rightarrow t}$ ,  $C_{max}$  increased, which might prolong the potency of ferulic acid and puerarin *in vivo*. The compounds in the single herb extract might play an important role in affecting the absorption of ferulic acid and puerarin. However, compatibility of Chinese medicinal formula could promote the ferulic acid and puerarin's absorption and subsequently enhanced their bioavailability in rats. The reason may be that something in the NDS has effects on several links of ADME (absorption, distribution, metabolism and elimination) of ferulic acid and puerarin

in rats, which lead to shorten  $T_{max}$  and increase  $C_{max}$  and  $AUC_{0\rightarrow t}$ , and the further ADME work of NDS would be considered as the obvious continuation of the current study.

## CONCLUSIONS

The present study demonstrated that that the pharmacokinetic process of active substance from Chinese medicinal formula was more complex and effective than that of the purified ingredient. Moreover, there were significant difference in pharmacokinetic parameters of ferulic acid and puerarin after oral administration of monomer, medicinal substance aqueous extract and NDS to rats. These differences revealed that compatibility of medicines could enhance its active ingredients' pharmacological potency *in vivo*, further indicating the reasonable compatibility of this recipe.

## ACKNOWLEDGEMENTS

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