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**Original Research Article**

# Studies of the pharmacokinetics of morroniside and loganin in rat after oral administration of raw and wine-processed *Corni fructus* by UPLC-QqQ-MS/MS

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## Abstract

***Purpose:*** *To study the pharmacokinetics of morroniside (MR) and loganin (LG) in rats after oral administration of raw and wine-processed Corni fructus by UPLC-QqQ-MS/MS.*
***Methods:*** *Arctiin (AT) was used as internal standard, and the plasma or tissue samples were extracted twice using ethyl acetate. Electrospray ionization (ESI) negative ion mode was used, and the multiple reaction monitoring mode (MRM) was set in acquisition mode. The extraction and detection method is supported by selectivity, sensitivity, precision, accuracy, stability, extraction, recovery and matrix effect. The non-atrioventricular model of das2.0 software was used to calculate the pharmacokinetic parameters.*
***Results:*** *The absorption rate of MR ($P_{Tmax}$=0.092) and LG ($P_{Tmax}$=0.092) in Corni Fructus after wine-processing was faster in rats. The mean residence time was longer, and distribution of MR ($P_{MRT0\sim t}$ = 0.294) and LG ($P_{MRT0\sim t}$ = 0.000) in wine-processed Corni Fructus group increased in liver and kidneys.*
***Conclusion:*** *The proposed method has been successfully validated and is suitable for studying the pharmacokinetics of the two analytes in rats.*

***Keywords:*** *Morroniside, Loganin, Corni Fructus, Wine-processed, Pharmacokinetics, Tissue distribution*

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## INTRODUCTION

*Corni Fructus* is the dry and mature pulp of *Cornus officinalis* (sieb.et Zucc.), which belongs to the Cornaceae family. Its maind function is the tonification of the liver and kidneys, astringent essence and solid retention [1] It was first published in Shen nong materia classic, and listed as a medium grade drug [2]. *Corni Fructus* is said to possess immense abilities in nourishing Yin, and also in stopping sweats. Research [3] has shown that the warming and tonifying effects on the liver and kidneys were enhanced in *Corni Fructus* after wine-processing. Presently, the existing literature on the processing mechanism of *Corni Fructus* is inadequate, and is mainly focused on the changes in chemical compounds before and after processing [4-6]. As one of the main effective compounds in *Corni Fructus*, iridoid glycosides have received more attention

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[7-9]. Preliminary studies revealed that the content of iridoid glycosides in Cornus officinalis decreased after wine-processing [10-12] However, the warming and tonifying effects on liver and kidneys increased. This could be attributed to iridoid glycosides, as the constituents moved into the blood, which could be responsible for their absorption in vivo after wine-processing, thus enhancing the tonifying effect on the liver and kidneys. Morroniside (MR) and loganin (LG) are the main iridoid glycosides components of medicinal value in *Corni Fructus* [13,14]. The contents of MR and LG are regarded as the processing optimization index in the first volume of Chinese Pharmacopoeia (2015 Edition) [1] and this processing principle was further expounded by the comparison between the pharmacokinetic characteristics of active ingredients in raw products, and that of processed products of traditional Chinese medicine in animals [15,16]. This study therefore attempts to analyze the pharmacokinetics of MR and LG after oral administration of raw and wine-processed *Corni Fructus*, so as to further clarify the processing mechanism of *Corni Fructus*.

## EXPERIMENTAL

### Materials and reagents

*Corni Fructus* was provided by the Xiuzheng Pharmaceutical Group Company Limited (No.20180409), as identified by Professor Yanjun Zhai of Liaoning University of Traditional Chinese Medicine. MR (No.16071405) and LG (No.16080704) were purchased from Chengdu Manster Biotechnology Co., Ltd. (Sichuan Province, China), with a purity level above 98 %). AT was self-made in our laboratory (it was first extracted from *Arctium lappa* L. rooted with ethanol, and silica gel column chromatography, eluted with ethyl acetate, and with solvent recovery from the eluent, Arctiin was obtained). HPLC detected the purity level to be more than 98 % Acetonitrile and formic acid were of chromatographic grade, and obtained from Merck (Germany). Other reagents were of analytical grade, and the water utilized was ultra-grade.

Male Sprague-Dawley (SD) rats (Animal License No. SCXK2015-0001) weighing 190 – 210 g were purchased from Liaoning Changsheng biotechnology Co., Ltd. (Benxi, China). The rats were housed for 7 days at ambient temperature (22 ± 2°C) with 12 h light/dark cycles before the experiment, and fasted for 24 h before gavage, while water was freely available. Animal experimentation was approved by the Animal Ethics Committee of Liaoning University of Traditional Chinese Medicine (no. 2017-125).

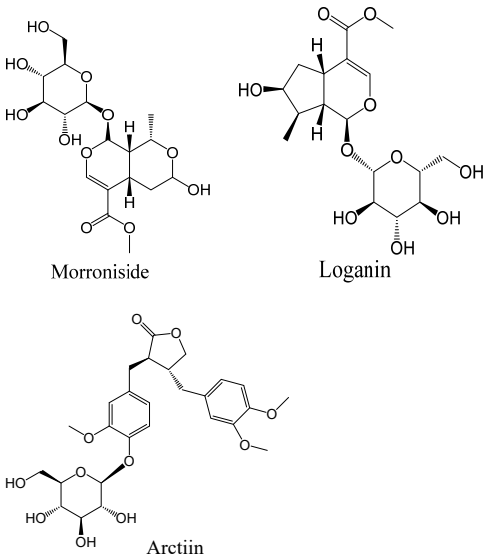


**Figure 1:** Chemical structures of MR, LG and AT

### Instruments and LC-MS conditions

Chromatographic analysis was performed in a Waters ACQUITY I-CLASS UPLC system (Waters Corporation, Milford, MA, USA), using an ACQUITY UPLC® BEH C18 column (50 mm × 2.1 mm, 1.7 µm, Waters). The mobile phase consisted of (A) acetonitrile and (B) water containing 0.1% formic acid, and the best elution conditions were as follows: 11 % A (0 − 1 min), 11 to 13.5 % A (1 − 2 min), 13.5 to 15 % A (2 − 2.5 min), 15 to 100 % A (2.5 − 3 min), (3 − 5 min) 100 %A, and then were immediately returned to the initial mobile phase composition. Flow rate was set at 0.3 mL/min while the temperature of the column and the auto-sampler room were set at 25 and 8 °C, respectively. The injection volume was 1 µL.

Mass spectrometry analysis was performed with a Waters XEVO TQD Triple Quadrupole equipped MS (Waters) with an electrospray ionization (ESI) in negative ion mode. The capillary voltage was set at 3.0 kV, the desolvation gas (N2) flow rate was set at 800 L/h, with a temperature of 400℃. The cone gas was set at 50 L/h. Selected multiple reaction monitoring (MRM), the precursor to product ion combinations of m/z 451.31→243.19, 435.31→227.12, 579.37→371.30, was used to detect MR, LG, and the internal standard (IS), AT respectively. (Table 1). MRM chromatograms of the three compounds are shown in Figure 2.

**Table 1:** MRM parameters of MR, LG, and the internal standard (IS), AT

| Analyte | Precursor Ion(m/z) | Product Ion(m/z) | Cone (V) | Collision (V) |
|---|---|---|---|---|
| MR | 451.31 | 243.19 | 28 | 16 |
| LG | 435.31 | 227.12 | 30 | 16 |
| AT(IS) | 579.37 | 371.30 | 38 | 18 |

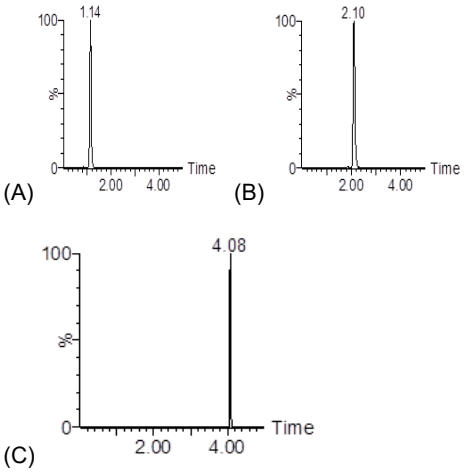


**Figure 2:** MRM chromatograms of (A) Morroniside, (B) Loganin, (C) Arctiin

**Preparation of wine-processed *Corni Fructus***

*Corni Fructus* (100 g) was mixed thoroughly with yellow rice wine (30 g), permeated for 1 hour, stewed for 5 h while keeping the *Corni Fructus* from touching the water at a pressure of 50 kPa, and then finally dried at a temperature of 50 °C.

**Preparation of extracts**

*Corni Fructus* (300 g) and wine-processed *Corni Fructus* (300 g) respectively were added into 15 times of water, heated with reflux extraction for 1 h, and filtered. Then the filter residue was added into 10 times of water, heated with reflux extraction for 1 h, and filtered. The filtrates were combined and concentrated into 300 mL. 1 mL contained 1 g of the crude drug. Morroniside and Loganin content was detected in the raw *Corni Fructus* at 0.923 and 0.770 %, and in the wine-processed *Corni Fructus* at 0.930 and 0.838 % by LC-MS.

**Preparation of reference standard, internal standard (IS) and quality control (QC) sample**

The reference solution, MR and LG were prepared by weighing the reference standard of the two compounds precisely, and dissolving them in methanol to yield concentrations of 0.208 mg/mL and 0.211 mg/mL, respectively. The reference standard solution of MR and LG were taken appropriately and mixed well, and then diluted in turn. The mixed reference series solutions with different concentration gradients were obtained. The IS solution of AT was prepared by weighing the reference of the compounds precisely and dissolving it in methanol to yield concentrations of 0.780 ng/mL. The mixed standard solutions of high, medium and low concentrations were dried with nitrogen, added to the blank plasma or tissues and mixed thoroughly. the QC samples were obtained, and all the solutions were stored at -20 °C.

**Method validation**

The method was validated with selectivity, linearity, sensitivity, precision, accuracy, extraction recovery, matrix effect and stability, in line with the FDA guidelines for validation of bioanalytical methods.

***Selectivity***

The selectivity was determined by comparing chromatograms of blank plasma (tissue) samples obtained from rats, with those of the corresponding plasma (tissue) samples spiked with MR, LG and IS, and plasma (tissue) samples after oral administration.

***Linearity and sensitivity***

A standard curve was constructed based on the peak area ratios of MR and LG to the IS, versus the concentrations of the compounds. The regression equations were obtained by applying weighted (1/x2) least-squares linear regression. The lower limit of quantification (LOQ) was calculated as the lowest concentration of the standard curve determined by the signal-to-noise ratio, which was generally higher than 5.

***Precision and accuracy***

The intra-assay and inter-assay precision was assessed by determining the QC samples at three concentrations for each compounds. Three (3) replicates of the QC plasma (tissue) samples were analyzed on the same day to assay the intra-day validation, and determined over three consecutive days to assay the inter-day validation. The precision was expressed as the relative standard deviation (RSD), and the accuracy as the relative error (RE).

***Extraction recovery and matrix effect***

The extraction of MR and LG at three different QC plasma (tissue) sample concentrations, were determined in six replicates. The matrix effects in

the approach were evaluated by comparing the peak areas of the compounds in the post-extraction spiked samples, with those of the standard solutions.

### *Stability*

The stabilities of MR and LG in rat plasma (tissue) were evaluated at three different QC concentrations, using six replicates under four conditions as follows: First, the QC samples were kept at 25 ℃ for 4 h. Next, the samples were treated to three freeze and thaw cycles, and in each cycle, the samples were stored at -20 ℃ for 24 h, then thawed unassisted at room temperature. When completely thawed, the samples were refrozen within 24 h. Third, the samples were kept at 4 ℃ for 12 h. Finally, the samples were kept at -80 ℃ for 15 days.

### Pharmacokinetics studies

### *Plasma*

Rats were randomly divided into 2 groups (raw *Corni Fructus* group, 20 g/kg; wine-processed *Corni Fructus* group, 20 g/kg; six in each time point). Plasma samples were collected into tubes from orbit at 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 360, 720, 144, 2160, and 2880 min after administration respectively, then immediately centrifuged at 3000×g for 15 min. The supernatant plasma layer was transferred into another tube and stored at -20℃ until analysis. The plasma sample (150 µL) was spiked with IS solution (70 µL) after thawing, extracted with ethyl acetate (1000 µL) by vortexing for 5 min, and centrifuged at 12000×g for 5 min. The supernatant layer was transferred into another tube, and the residue was extracted with ethyl acetate (1000 µL) by vortexing for 5 min, and centrifuged at 12000×g for 5 min, again. The supernatant layer of two time points were combined, then evaporated to dryness under a gentle stream of nitrogen. The residue was reconstituted in methanol (100 µL), vortexed for 30 s, and centrifuged at 12000×g for 5 min, the supernatant was filtrated through a 0.22 µm microporous membrane, then injected into the UPLC-MS/MS system for analysis.

### *Tissue*

The tissue distribution of *Corni Fructus* (20 g/kg) and wine-processed *Corni Fructus* (20 g/kg) after oral administration was investigated in rats at 0.25, 0.5, 1.5, 3 and 6 h, by collecting tissue samples from the liver, spleen, lung, kidneys, stomach, small intestine, and large intestine. The tissues were added to 3 times the normal saline, and homogenate for 2 min. They were then centrifuged at 3000×g for 5 min, and the supernatant layer was transferred into another tube. Following the same method of plasma handling, the supernatant layer was then injected into the UPLC-MS/MS system for analysis.

### Statistical analysis

The non-atrioventricular model of das2.0 software was used to calculate the pharmacokinetic parameters while SPSS 17.0 software was used for statistical analysis. Gender differences in $AUC_{0-t}$, AUC0-∞, $T_{1/2}$ and $C_{max}$ were tested using t-test.

## RESULTS

### Validation results

### *Selectivity*

Figure 3 demonstrates that there was no major interference from endogenous compounds in the analysis of the compounds, and good selectivity was achieved. The retention time of MR, LG, and the IS were approximately 1.14, 2.10 and 4.08 min, respectively.

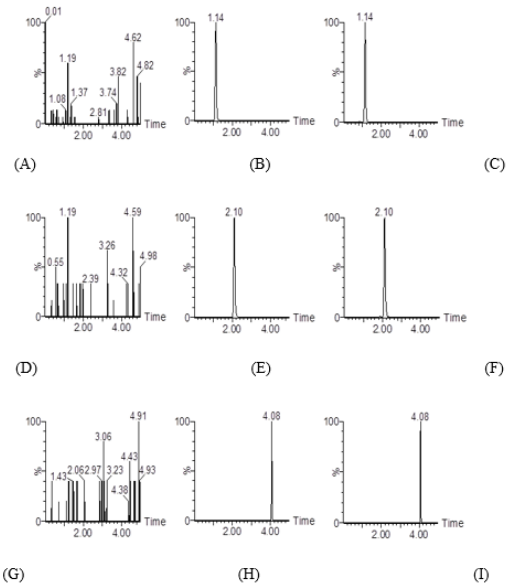


**Figure 3:** UPLC chromatograms of plasma sample. *(A). Blank plasma of morroniside; (B). High concentration QC sample of morroniside; (C). Plasma taken 15 min after oral administration of morroniside; (D). Blank plasma of loganin; (E). High concentration QC sample of loganin; (F). Plasma taken 15 min after oral administration of loganin; (G). Blank plasma of arctiin; (H). High concentration QC sample of arctiin; (I). Plasma taken 15 min after oral administration of arctiin*

### *Linearity and sensitivity*

All the linear correlations of MR and LG in rat plasma or tissues displayed good linear relationships respectively (r > 0.99). The slope and intercept of the calibration graphs were calculated by weighted (1/x2) least-squares linear regression. The lower limit of quantification (LOQ) was determined as the lowest concentration of the standard curve, determined by the signal-to-noise ratio, which was generally higher than 5, were 2 ng/mL for MR, and 4 ng/mL for LG (Table 2).

### *Precision and accuracy*

The intra and inter-day precision were satisfactory, both RSD and RE values were in the range of ±15 % (Table 3).

### *Extraction recovery and matrix effect*

The extraction recoveries of MR and LG were in the range of 53.2 ~ 57.6 % and 62.6 ~ 67.5 %, while RSD were less than 7.4 % (Table 3), suggesting that the precision and accuracy of this method was acceptable. The matrix effects of the two compounds in the three QC concentrations were in the range of 84.4 ~ 93.7% and 98.3 ~ 107.3 %. RSD were less than 7.2 % (Table 3), which indicated that the matrix effect was negligible.

### Stability

In four conditions, MR and LG were no major degradation, RSD were less than 11.4% (Table 5), which indicated that the Stability was good.

**Table 2:** Regression, linear range, and LLOQ of MR and LG in rat plasm and tissue

| Analyte | Position | Range (μg/mL) | Calibration curve | r | LLOQ (ng/mL) |
|---|---|---|---|---|---|
| MR | Plasma | 0.1632~20.1917 | *Y*=879.731*X*+26.9096 | 0.9985 | 2 |
| | Liver | 0.0813~10.400 | *Y*=1.2806*X*-0.03398 | 0.9943 | 2 |
| | Spleen | 0.0813~41.600 | *Y*=0.7855*X*+0.00534 | 0.9980 | 2 |
| | Lung | 0.0813~20.800 | *Y*=0.9502*X*+0.00402 | 0.9927 | 2 |
| | Kidney | 0.0813~41.600 | *Y*=0.8652*X*+0.01356 | 0.9979 | 2 |
| | Stomach | 0.0813~41.600 | *Y*=1.1321*X*-0.01137 | 0.9965 | 2 |
| | S i | 0.0813~41.600 | *Y*=0.8963*X*-0.00785 | 0.9961 | 2 |
| | L I | 0.0813~41.600 | *Y*=0.8559*X*+0.00190 | 0.9967 | 2 |
| LG | Plasma | 0.1676~20.1386 | *Y*=405.342*X*+23.6757 | 0.9964 | 4 |
| | Liver | 0.0825~10.550 | *Y*=0.4247*X*-0.00992 | 0.9933 | 4 |
| | Spleen | 0.0825~42.200 | *Y*=0.3392*X*-0.05456 | 0.9968 | 4 |
| | Lung | 0.0825~21.100 | *Y*=0.3636*X*-0.00029 | 0.9984 | 4 |
| | Kidney | 0.0825~42.200 | *Y*=0.3520*X*-0.00081 | 0.9923 | 4 |
| | Stomach | 0.0825~42.200 | *Y*=0.0427*X*-0.00023 | 0.9965 | 4 |
| | S I | 0.0825~42.200 | *Y*=0.3577*X*+0.00289 | 0.9950 | 4 |
| | L I | 0.0825~42.200 | *Y*=0.3624*X*-0.00683 | 0.9914 | 4 |

**Table 3:** Precision and accuracy of MR and LG with different concentrations in plasma (n=6)

| Analyte | Added C (μg/mL) | Intra-day | | | Inter-day | | |
|---|---|---|---|---|---|---|---|
| | | Measured C (μg/mL) | Precision (% RSD) | Accuracy (% RE) | Measured C (μg/mL) | Precision (% RSD) | Accuracy (% RE) |
| MR | 0.416 | 0.37±0.01 | 3.14 | -10.06 | 0.39±0.04 | 9.74 | -6.41 |
| | 2.600 | 2.65±0.14 | 5.23 | 1.98 | 2.89±0.06 | 1.91 | 11.16 |
| | 15.600 | 16.26±1.22 | 7.52 | 4.25 | 16.72±0.98 | 5.88 | 7.18 |
| LG | 0.422 | 0.39±0.04 | 9.38 | -8.24 | 0.39±0.04 | 9.63 | -7.09 |
| | 2.638 | 2.80±0.16 | 5.84 | 6.24 | 2.98±0.13 | 4.28 | 13.06 |
| | 15.825 | 17.05±0.75 | 4.39 | 7.77 | 17.83±1.44 | 8.10 | 12.64 |

**Table 4:** Extraction recovery and matrix effects of MR and LG with different concentrations in plasma (n = 6)

| Analyte | Concentration (μg/mL) | Extraction recovery (RSD)/% | Matrix effect (RSD)/% |
|---|---|---|---|
| MR | 0.416 | 53.15(3.60) | 93.66(3.16) |
| | 2.600 | 56.29(4.85) | 84.41(7.16) |
| | 15.600 | 57.59(5.88) | 90.43(4.77) |
| LG | 0.422 | 62.61(7.45) | 107.29(4.93) |
| | 2.638 | 67.05(6.02) | 91.39(5.21) |
| | 15.825 | 67.53(6.62) | 98.25(5.99) |

**Table 5:** Stability of MR and LG with different concentrations (n=6)

| Analyte | Concen-tration (μg/mL) | 4 h in room temperature | | -20 ℃ for 3 freeze-thaw cycles | | 4 ℃ for12 h | | -80 ℃ for 15 days | |
|---|---|---|---|---|---|---|---|---|---|
| | | Accuracy (%) | RSD (%) | Accuracy (%) | RSD (%) | Accuracy (%) | RSD (%) | Accuracy (%) | RSD (%) |
| MR | 0.42 | 91.95 | 7.16 | 84.71 | 10.09 | 85.60 | 8.79 | 92.64 | 3.26 |
| | 2.60 | 101.93 | 6.78 | 97.09 | 5.71 | 95.15 | 2.51 | 93.37 | 2.46 |
| | 15.60 | 96.65 | 6.30 | 95.40 | 6.08 | 96.47 | 2.01 | 94.57 | 9.64 |
| LG | 0.42 | 95.64 | 7.73 | 92.80 | 6.45 | 90.78 | 11.00 | 99.59 | 11.38 |
| | 2.64 | 105.34 | 6.28 | 103.24 | 6.69 | 99.67 | 6.90 | 103.07 | 5.55 |
| | 15.83 | 97.78 | 7.07 | 90.22 | 9.43 | 91.75 | 3.32 | 95.42 | 8.92 |

## Pharmacokinetics

### *Plasma*

The corresponding pharmacokinetic parameters in rat plasma are summarized in Table 6. Plasma concentration-time curves are showed in the Figure 3.

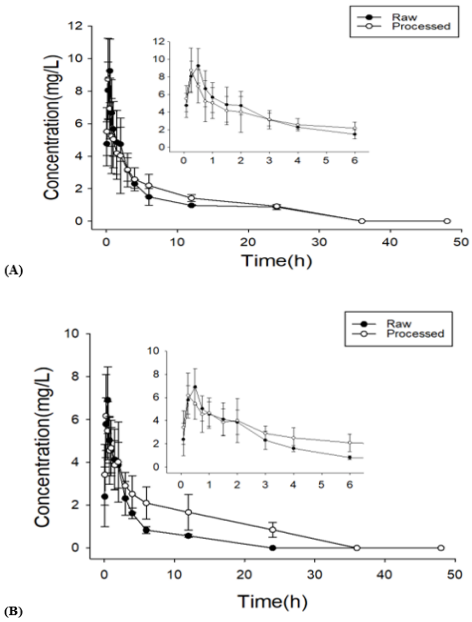


**Figure 3:** Plasma concentration-time curve of MR and LG after oral administration of raw and wine-processed *Corni Fructus* in rats (mean ± SD, n = 6). ***Note:*** A = MR; B = LG

### *Tissues*

The corresponding tissue content of raw *Corni Fructus* and wine-processed *Corni Fructus* is summarized in Figure 4.

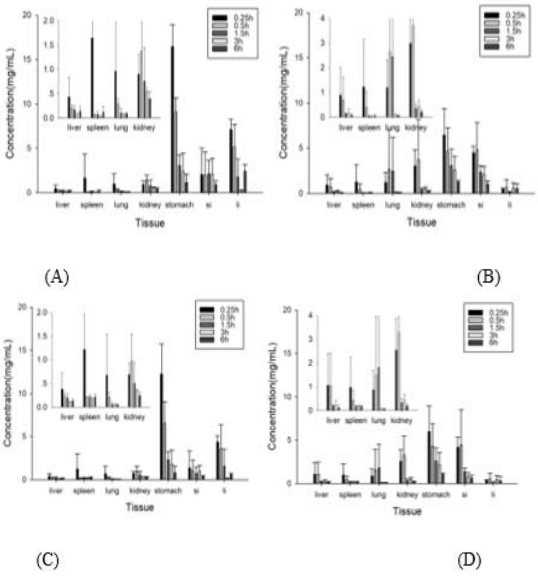


**Figure 4:** Concentration of MR and LG in different tissues at different time points after oral administration of raw and wine-processed *Corni Fructus. MR of raw Corni Fructus; (B) LG of raw Corni fructus; (C) MR of wine-processed Corni fructus; (D) LG of wine-processed Corni fructus*

**Table 6:** Pharmacokinetic parameters of MR and LG after oral administration of raw and wine-processed *Corni Fructus* ( $\overline{x} \pm S$ ,n=6)

| Parameter | MR | | LG | |
|---|---|---|---|---|
| | raw | processed | raw | processed |
| $C_{max}$/mg·L$^{-1}$ | 9.85±1.49 | 8.80±2.50 | 7.27±1.17 | 6.31±1.89 |
| $T_{max}$/h | 0.42±0.13 | 0.29±0.10 | 0.46±0.10 | 0.33±0.13 |
| $t_{1/2}$/h | 3.40±0.04 | 3.25±0.06$^{\Delta}$ | 3.68±0.06 | 3.25±0.19$^{\Delta}$ |
| $AUC_{0\sim t}$/mg·h·L$^{-1}$ | 46.10±3.35 | 52.15±5.51$^{\Delta}$ | 24.37±2.89 | 51.27±15.00$^{\Delta}$ |
| $AUC_{0\sim\infty}$/mg·h·L$^{-1}$ | 46.11±3.35 | 52.16±5.51$^{\Delta}$ | 24.37±2.89 | 51.27±15.00$^{\Delta}$ |
| $MRT_{0\sim t}$/h | 9.33±0.79 | 9.78±0.60 | 4.58±0.49 | 9.75±1.22$^{\Delta}$ |

## DISCUSSION

In the electrospray ionization positive ion mode, the response values of MR and LG were very low, and therefore could not be used for quantitative analysis. In the negative ion mode, MR and LG had high response values, and so the negative ion mode was used for analysis. It has been reported that the content of MR and LG in *Corni fructus* is lower after processing [10-12,17-19]. However, the extraction rate of MR and LG in the decoction of raw *Corni fructus* is lower than that of wine-processed *Corni fructus* [19]. In this experiment, LC-MS was used to determine the content of MR and LG in raw and wine-processed *Corni Fructus* extract. The results showed that the content of MR and LG in wine-processed *Corni fructus* extract was slightly higher than that of raw *Corni fructus* extract.

The plasma study also showed that both MR and LG in wine-processed *Corni fructus* could reach maximum plasma concentration rapidly, as the absorption speed was faster, the concentration-time(C-T) curves were significantly higher than that in raw *Corni fructus*, and the average retention time was longer. It may be that the effective absorption of ingredients was promoted, the Tmax of MR and LG *in vivo* was shortened, and residence time *in vivo* and the exertion of drug effect was prolonged by the wine-processed *Corni Fructus*. This result may be one of the reasons for the enhancement of liver and kidney tonic function, due to the effects of wine-processed *Corni fructus*.

It can be observed in Figure 4 that the MR and LG in raw and wine-processed *Cornus officinalis* can be absorbed quickly after oral administration. After 0.25 h of administration, components of MR and LG were detected in vivo. Meanwhile, it was found in the preliminary experiment that the MR and LG could not be detected in the brain and heart tissues, as these two components may not pass through the blood-brain barrier. MR and LG were detected in the liver, spleen, lung, kidneys, stomach, and small and large intestines, but were more distributed in stomach, small and large intestinal tissues. Compared with raw *Cornus officinalis*, the distribution of MR and LG in wine-processed *Corni fructus* in stomach and large intestine tissues decreased significantly. However, in small intestine tissues, the distribution increased significantly, in liver, kidney and lung, increased slightly and in spleen decreased slightly. It showed that the absorption rate could be promoted after wine-processing, and its bioavailability is enhanced. Research [19,20] shows that the effect of wine-processed *Corni Fructus* on tonifying the liver and kidneys is enhanced by the power of wine, which is also consistent with the conclusion that the distribution of MR and LG in the liver and kidneys is increased after wine-processing.

### CONCLUSION

A sensitive and selective UPLC-QqQ-MS method for the simultaneous determination of morroniside and loganin from *Corni fructus* in rat plasma and tissue has been developed and validated in this study. These results might be useful in demonstrating possible processing mechanisms and clinical application of *Corni fructus*.

## DECLARATIONS

### *Acknowledgement*

This research was funded by subject of study on processing standardization of Liuwei Dihuang capsule from Xiuzheng Pharmaceutical Group Company Limited in China, (Grant no. ZYBZH-C-JL-24-01).

### *Conflict of interest*

No conflict of interest is associated with this work.

### *Contribution of authors*

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors, Chengguo Ju supervised the experiments and acquired funding for the research. Wei Wang designed and performed the experiments, and wrote the manuscript. Xuechun Wang assisted in the experiments. Qiang Zhang and Ru Jia bred rats and collected blood. Chunjie Du operated the instruments.

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