Citri Unshiu Pericarpium prolongs mean residence time of guaiacol after oral administration of wood creosote pill to rats

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In Japan, wood creosote pills containing four herbal drugs have been used to treat food poisoning and diarrhea. It was previously reported that among the four herbal drugs used, Citri Unshiu Pericarpium (CUP2, Chinpi in Japanese) plays an important role in sustaining the dissolution of the active constituents of wood creosote (guaiacol) from the pill. To clarify the pharmacological role of CUP2 in these pills, pharmacokinetic interactions between CUP2 and guaiacol were examined after oral administration of a wood creosote pill containing four herbal drugs (P4R) to rats. The mean residence time (MRT) of guaiacol in the P4R-treated rats was significantly longer than that of the rats treated with a variant pill (P4R with a reduced amount of CUP2). There were no significant differences in the area under the mean concentration versus time curve from zero to 5 h (AUC) between the two groups. The prolongation effect of CUP2 on the MRT of guaiacol was thought to be partly due to the mean dissolution time (MDT) of guaiacol from the pill. Since a long MRT and MDT are indexes of the duration effects of drugs, CUP2 might be a good adjuvant for prolonging anti-diarrhea effects after oral administrations of wood creosote pills.

Key words wood creosote, guaiacol, mean residence time, mean dissolution time, pharmacokinetic drug interaction, Citrus unshiu.

Abbreviations AUC, area under the concentration versus time curve; Cmax, maximum plasma concentration; CUP, Citri Unshiu Pericarpium; CUP2, CUP preserved for 2 years; GAM, Gambir; GLR, Glycyrrhizae Radix; ka, dissolution rate constant; MDT, mean residence time; MRT, mean dissolution time; P4R, wood creosote pill for rat containing four herbal drugs; P4R-CUP2, P4R without CUP2; P4R-1/2CUP2, P4R without one-half amount of CUP2; PHC, Phellodendri Cortex; SIM, selected ion monitoring; TIC, total ion chromatogram; Tmax, time to reach maximum plasma concentration.

Introduction

The wood creosote (or beechwood creosote) pill has been used in Europe and Japan for the treatment of food poisoning and diarrhea. It contains a significant quantity of phenolic compounds such as guaiacol and p-creosol, which have been shown to suppress intestinal smooth muscle contractions and fluid secretions induced by enterotoxins thus participating in the anti-diarrhea effect of creosote. In Japan, a wood creosote pill containing four herbal drugs, Glycyrrhizae Radix (GLR, Kanzo in Japanese), Gambir (GAM, Asen-yaku in Japanese), Phellodendri Cortex (PHC, Oubaku in Japanese), and Citri Unshiu Pericarpium (CUP, Chinpi in Japanese), has been widely used in self-medication under the name of "Seiro-gan".

Although the wood creosote pill has a long medicinal history, little is known about the pharmaceutical role of its herbal components on the bioavailability of anti-diarrhea ingredients (guaiacol) in wood creosote. Recently, the authors reported that among the four herbal drugs prescribed in the wood creosote pill, CUP retarded guaiacol release from the pill (for human size: 220 mg) in vitro dissolution tests. In the present study, the effects of CUP on pharmacokinetic parameters including the mean residence time (MRT) of guaiacol were examined after oral administration of a small pill (4.8 mg) to rats. Furthermore, the mean dissolution time (MDT) of guaiacol from these pills was examined by varying the amount of CUP.

Materials and Methods

Wood creosote, herbal drugs and chemicals. A wood creosote (Taiko Teco Co., Ltd, Osaka, Japan) containing 27.4 ± 0.1% guaiacol, 19.5 ± 0.1% creosol, and 9.9 ± 0.1% phenol as determined previously was used. As previously reported, four crude drug powders (GAM, GLR, PHC and CUP) were used. Of the CUP varieties available, Chinese CUP preserved for 2 years (CUP2) was used, the botanical origin of which was estimated to be Citrus unshiu according to its reported HPLC-profiles. The particle size distributions and major ingredients (catechin, glycyrrhizin, berberine and nobiletin) of these powders were described previously. Voucher specimens of these herbal drugs and their powders were deposited in the Research Institute of Taiko Pharmaceutical Co., Ltd. The chemicals and authentic compounds used were as those described previously.

Preparation of wood creosote pills. Glycerin (2 g) fol-
lowed by water (11 ml) then wood creosote (8 g) were added to a mixture of the four herbal drug powders, GAM (4 g), PHC (6 g), GLR (3 g) and CUP2 (6 g). The combination ratio of creosote to the four drugs was analogous to that of commercial "Seiro-gan". The resultant paste was kneced in a porcelain mortar for 5 min and then made into pills (P4R) of approximately 4.8 mg (diameter 2 mm) containing 286 ± 8 µg of guaiacol for in vivo experiments using rats. Two variant P4R pills containing 3 g of CUP2 (P4R-1/2CUP2) and without CUP2 (P4R-CUP2), respectively were also prepared.

**Viscosity of the paste and dissolubility time of the pills.** Pill viscosity (Pascal · sec, Pa·s) was determined using a viscometer (Model TVE-20H, T-bar stage Type T-E, Toki Sangyo Co., Ltd. Japan) at room temperature for 180 sec, at 0.3 rpm and with a full-scale torques of 102.4 Pa·s. Dissolvibility time (min) was determined as the time it took for the pill to become completely dissolved. Since the small pills dissolved gradually without disintegration, ordinal dissolubility time was not determined.

**Dissolution of guaiacol from the pills.** The dissolution rate (%) of guaiacol from three pills (P4R, P4R-1/2CUP2 and P4R-CUP2) was determined according to the JP XIV method using a dissolution tester (NTR-6100, Toyama Sangyo Co., Ltd. Japan) as previously reported. Briefly, six pills were placed in dissolution medium (500 ml; No.1 solution of JP XIV) at 37 ± 0.5 °C and stirred with a paddle rotating at 100 rpm. One-ml sample solutions were withdrawn after 5, 10, 20, 40 and 60 min and equivalent volumes of fresh medium were added to maintain the volume of the dissolution medium. The solution was filtered through a 0.45 µm membrane filter and the filtrate (500 µl) was mixed with 20 µl of internal standard solution (10 ng/µl of 2-fluorophenol) and 500 µl of ethyl acetate (AcOEt). The mixture was vortexed for 3 min and centrifuged at 5000 rpm for 3 min, after which the AcOEt soluble portion (1 µl) was injected into the GC/MS system (conditions are shown in the legend of Fig. 3).

**Pharmacokinetic investigation.** Pharmacokinetics of the guaiacol was carried out as previously reported. Ten-week old male Wistar ST rats were purchased from Japan SLC Inc., Hamamatsu, Japan. Prior to use, they were housed for 60 days in an environmentally controlled facility with diurnal light cycling and free access to food and water. Rats weighing 400 to 450g were used throughout the study. After fasting overnight (18 hr), rats were anesthetized with an intraperitoneal injection of sodium pentoarbital (30 mg/kg) and cannulated into the jugular vein. A gastric sonde, the tip of which was stuck to a P4R pill was inserted into the stomach and administered by injecting 0.3 ml of distilled water. Blood samples of approximately 0.5 ml were collected from the cannula at 0, 5, 10, 20, 30, 60, 90, 120, 180, 240 and 300 min after pill administration and the plasma was immediately separated from the heparinized blood by centrifugation, which was stored at -20 °C until analysis. Similar experiments were also conducted using rats with diarrhea induced by oral administrations of castor oil (5.6 ml/kg) 1 h before pill administration. All animal experiments were carried out in accordance with the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Science.

**Plasma guaiacol.** An aliquot of plasma (150 µl) was mixed with Helix pomatia sulfatase (1.8 units/µl, EC 3.1.6.1, type H-1 containing β-glucuronidase activity; Sigma, Japan) and sodium acetate buffer (4 mol/l, pH 5.0), and incubated at 37 °C for 2 h. One N HCl (60 µl), 20 µl of 2-fluorophenol solution (10 ng/µl, internal standard) and AcOEt (1 ml) were added to the reaction mixture, which was then vortexed for 3 min and centrifuged at 5000 rpm for 3 min. The AcOEt soluble portion was analyzed by GC/MS using the conditions as shown in the legend of Fig. 3. The standard curve for determination of plasma guaiacol concentrations was as follows: Y = 0.0005X + 0.0086, r =0.999 (Y: peak area ratios, X: guaiacol ng/ml); detection limit: 100 ng/ml, recovery: 80%

The maximum plasma concentration (Cmax) and time required to reach Cmax (tmax) were determined directly from actual plasma guaiacol levels. The area under the mean concentration versus time curve from zero to 5 h (AUC<sub>0-5</sub>) and the MRT were calculated using WinNonlin (Pharsight Co., USA).

**Statistics.** Results are presented as the mean ± S.D. and were compared using the Student's t-test and Williams test. Probability (p) values of less than 0.05 were considered significant.

**Results**

**Viscosity and dissolubility time of the pills (Fig. 1).** Fig. 1 shows that the viscosity of P4R (29.4 ± 1.2 Pa·s) was significantly (p<0.05) larger than those of P4R-1/2CUP2 (15.6 ± 1.1 Pa·s) and P4R-CUP2 (6.4 ± 0.6 Pa·s). The dissolubility time of P4R (56 ± 2 hr) also
Fig. 2. Dissolution rates of guaiacol from wood creosote pills
Each value represents the mean ± S.D. (n=6). a) p<0.05 vs P4R (by Williams test), b) p<0.05 vs P4R-1/2CUP2
Pill abbreviations are shown in the legend of Fig. 1.
Guaiacol analysis are shown in the legend of Fig. 3.

Table 1 Dissolution parameters of guaiacol from wood creosote pills

<table>
<thead>
<tr>
<th>Dissolution parameters</th>
<th>kd (min⁻¹)</th>
<th>MDT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4R</td>
<td>8.7 ± 0.5</td>
<td>12.6 ± 1.1</td>
</tr>
<tr>
<td>P4R-1/2CUP2</td>
<td>9.8 ± 0.8  a)</td>
<td>10.1 ± 1.2 a)</td>
</tr>
<tr>
<td>P4R-CUP2</td>
<td>14.0 ± 1.1 a,b)</td>
<td>7.1 ± 1.1 a,b)</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n=6). a) p<0.05 vs P4R (by Williams test), b) p<0.05 vs P4R-1/2CUP2

Dissolution profiles of guaiacol (Fig. 2 and Table 1). Fig. 2 shows that the dissolution rate of guaiacol from P4R-CUP2 was significantly (p<0.05) higher than those from P4R-1/2CUP2 and P4R at 5, 10 and 20 min. Table 1 shows that the kd and MDT of guaiacol from the two variant pills (P4R-1/2CUP2 and P4R-CUP2) was significantly (p<0.05) different from that of the original P4R.

Plasma guaiacol concentrations in normal rats (Figs. 3 and 4, Table 2). Fig. 3 shows the GC chromatograms of phenol (m/z 94), guaiacol (m/z 124) and p-creosol (m/z 138) in the AcOEt soluble portion of the sulfate-treated serum obtained 1 h after oral administration of pills. The peaks for the three major ingredients and 2-fluorophenol (IS, m/z 112) were clearly detected in the selected ion monitoring (SIM) mode, although they were not detected in the total ion chromatogram (TIC).

Fig. 4 shows the plasma concentrations of guaiacol versus time after a single oral administration of a pill containing 286 ± 8 μg of guaiacol to normal rats. The total (unconjugated and conjugated: glucuronide and sulfate forms) concentration of guaiacol in the plasma was determined. Guaiacol appeared in the plasma 5 min after administration, reached Cmax (about 1.3 - 2.0 μg/ml) between 45 and 115 min, and then gradually decreased below the detection limit at 5 h.

Table 2 shows that the Tmax and MRT of guaiacol from P4R-CUP2 were significantly small compared with those from original P4R, while the Cmax from P4R-CUP2 was significantly larger than that from P4R. Although the AUC(0-5h) was somewhat lower in the 4-CUP2 pill group, there were no significant differences in the AUC(0-5h) of the three groups.

Plasma guaiacol concentrations in the diarrhea rats (Fig. 4 and Table 2). Fig. 4 shows the mean time courses of plasma guaiacol concentrations in the castor oil-treated rats, in which diarrhea was observed from 1 h after castor oil treatment to the end of blood sampling time (5 h after castor oil treatment). The plasma concentrations of guaiacol from the three pill groups in diarrhea rats were similar with those obtained in normal rats, however, the Tmax of guaiacol was small compared with that of the normal rats.

Table 2 shows that the Tmax, AUC(0-5h) and MRT levels of the diarrhea rats were much lower than those of the normal rats, however, the Cmax was higher in the diarrhea rats than the normal rats.

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Plasma guaiacol concentrations in normal rats (Figs. 3 and 4, and Table 2). Fig. 3 shows the GC chromatograms of phenol (m/z 94), guaiacol (m/z 124) and p-creosol (m/z 138) in the AcOEt soluble portion of the sulfate-treated serum obtained 1 h after oral administration of wood creosote pills. The peaks for the three major ingredients and 2-fluorophenol (IS, m/z 112) were clearly detected in the selected ion monitoring (SIM) mode, although they were not detected in the total ion chromatogram (TIC).

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Table 2 shows that the Tmax, AUC(0-5h) and MRT levels of the diarrhea rats were much lower than those of the normal rats, however, the Cmax was higher in the diarrhea rats than the normal rats.
Bioavailability of guaiacol from wood creosote pill

![Graph](image)

**Fig. 4.** Plasma guaiacol concentrations after oral administration of wood creosote pills to castor oil-induced diarrhea (A) and normal rats (B). Each total (conjugated and unconjugated) guaiacol concentration represents the mean ± S.D. (n=6). a) p<0.05 vs P4R (by Williams test), b) p<0.05 vs P4R-1/CUP2. ●: P4R; △: P4R-1/CUP2; ○: P4R-CUP2.

Pill abbreviations are shown in the legend of Fig.1.

**Table 2** Pharmacokinetic parameters of guaiacol from wood creosote pills in rats

<table>
<thead>
<tr>
<th></th>
<th>Tmax (h)</th>
<th>Cmax (µg/ml)</th>
<th>AUC0-24 (µg・h/ml)</th>
<th>MRT (h)</th>
</tr>
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<tbody>
<tr>
<td>Normal rats:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4R</td>
<td>1.92 ± 0.20</td>
<td>1.30 ± 0.06</td>
<td>3.74 ± 0.31</td>
<td>2.22 ± 0.19</td>
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<tr>
<td>P4R-1/CUP2</td>
<td>1.08 ± 0.20</td>
<td>1.75 ± 0.17</td>
<td>3.87 ± 0.67</td>
<td>1.50 ± 0.14</td>
</tr>
<tr>
<td>P4R-CUP2</td>
<td>0.75 ± 0.27</td>
<td>1.99 ± 0.20</td>
<td>3.34 ± 0.69</td>
<td>1.23 ± 0.22</td>
</tr>
<tr>
<td>Diarrhea rats:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4R</td>
<td>0.92 ± 0.19</td>
<td>1.93 ± 0.29</td>
<td>3.75 ± 1.11</td>
<td>1.50 ± 0.23</td>
</tr>
<tr>
<td>(48 ± 11%)</td>
<td>(142 ± 36%)</td>
<td>(100 ± 32%)</td>
<td>(67 ± 11%)</td>
<td></td>
</tr>
<tr>
<td>P4R-1/CUP2</td>
<td>0.58 ± 0.19</td>
<td>1.98 ± 0.14</td>
<td>3.33 ± 0.20</td>
<td>1.45 ± 0.08</td>
</tr>
<tr>
<td>(54 ± 19%)</td>
<td>(113 ± 9%)</td>
<td>(97 ± 6%)</td>
<td>(99 ± 6%)</td>
<td></td>
</tr>
<tr>
<td>P4R-CUP2</td>
<td>0.28 ± 0.08</td>
<td>2.58 ± 0.40</td>
<td>2.40 ± 0.62</td>
<td>1.01 ± 0.36</td>
</tr>
<tr>
<td>(37 ± 11%)</td>
<td>(130 ± 24%)</td>
<td>(72 ± 20%)</td>
<td>(82 ± 32%)</td>
<td></td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n=6). a) p<0.05 vs P4R in normal rats, b) p<0.05 vs P4R in diarrhea rats, c) P<0.05, significantly different from the pills in the diarrhea rats and the corresponding pills in the normal rats. (a) and (b): by Williams test. Parentheses show the percentage of the corresponding value in normal rats.

Tmax: time required to reach Cmax. Cmax: maximum plasma concentration. AUC0-24: areas under the plasma concentration curves from zero to 5hr. MRT: mean residence time.

**Discussion**

Recently, the interactions that occur between herbal and chemical drugs during medicinal treatments have been attracting much attention. Drug-drug interactions are also important for the production and improvement of formulations containing multiple drugs. The authors have been investigating the interactions between the herbal drugs prescribed in wood creosote pills and the active constituents of wood creosote (guaiacol). It is clear that the MDT of guaiacol from wood creosote pills containing four herbal drugs is delayed compared with that from pills containing wood creosote only. Of the four herbal drugs, CUP2 (Chinpi in Japanese) has been shown to play a crucial role in the MDT duration of guaiacol. In the present paper, the effects of CUP2 on the pharmacokinetic parameters of guaiacol from wood creosote pills were examined after oral administration to rats. To achieve this, small rat-sized pills (P4R: approximately 4.8 mg and containing 286 ± 8 µg of...
guaiacol) and two variant pills (P4R-1/2CUP2 and P4R-CUP2) were prepared.

As seen in Fig.1, the CUP2 prescribed in P4R increased the viscosity and dissolubility time in proportion to the amount of CUP2. Fig. 2 and Table 2 suggest that CUP2 delayed the dissolution of guaiacol from these pills by lengthening the dissolubility time. The MDT of guaiacol is an important standard for evaluating the duration of the effects of wood creosote pills.

Total plasma (conjugated and unconjugated) guaiacol concentrations after hydrolyzation with sulfatase containing β-glucuronidase were analyzed by gas chromatography with mass selective detection as previously reported. Table 2 summarizes the changes in the pharmacokinetic parameters of guaiacol following administration of pills with (P4R: approximately 0.64 mg guaiacol/kg rat) and without CUP2 (P4R-CUP2). Although no changes in the AUC<sub>0,inf</sub> of guaiacol were observed from the three pills, the T<sub>max</sub> and MRT of guaiacol from the two variant pills (P4R-1/2CUP2 and P4R-CUP2) were shorter than that of the original P4R.

Similar decreases in the T<sub>max</sub> and MRT of guaiacol were observed in the diarrhea rats with the two variant pills. These results might be due to the differences in the pills with or without CUP2. The changes in MRT during the pharmacokinetic in vivo study correlates well with the prolongation effect of CUP2 on the MDT of guaiacol from the pills observed during the in vitro dissolution tests (Table 1). The duration of MRT as well as the MDT of guaiacol with CUP2 significantly influence the long-term anti-diarrhea effect of wood creosote pills containing four herbal drugs. The beneficial effects of CUP2 observed in the present study are supporting evidence that CUP2 is prescribed in wood creosote pills. The reported protective effects of the CUP2 ingredient (nobiletin) on the gastric mucosal barrier is also useful as a material in wood creosote pills for the treatment of digestive disorders.

In the diarrhea rats studied here, a decreased T<sub>max</sub> and increased C<sub>max</sub> of guaiacol were observed due to the rapid passing of mushy stools compared with the normal rats. These results are consistent with the previously reported results, in which the C<sub>max</sub> of nepatadan was significantly increased in castor oil-treated rats. The anti-diarrhea effects of the three types of pills were not observed in the present castor oil-treated diarrhea rats. Autonomic nervous function as a vermicular motion of the intestinal tract might be affected by treatment with pentobarbital due to its reduction effects on catecholamine. In the present study, pentobarbital was used as an anesthetic during insertion of the cannula; therefore, further additional studies are necessary to clarify the anti-diarrhea effects of P4R in pentobarbital un-treated rats.

The results obtained from this pharmacokinetic study of P4R (about 2.2 mg wood creosote/kg) in normal rats were compared with those of forty healthy volunteers (32 men and 8 women aged 19-42 years) orally administered with wood creosote alone (135 mg: about 2.3 mg/kg, human daily dose). Although there were no changes in the AUC values of guaiacol (normal rats: 3.74 ± 0.3; human volunteers: 3.62 ± 0.43 µg·h/ml), the T<sub>max</sub> and MRT values of the guaiacol in normal rats (1.92 ± 0.20 h and 2.22 h) was longer than that of the humans (0.50 ± 0.0 h and 1.26 h). The presence of herbal drugs (especially CUP2) in P4R might be one of the likely causes for the increase in the T<sub>max</sub> and MRT of guaiacol in the rat study.

In summary, this report deals with the effects of CUP2 prescribed in wood creosote pills on the pharmacokinetic parameters of guaiacol after a single oral administration of a pill to rats. In the variant pills (reduced amounts or absence of CUP2), a marked decrease in the MRT of guaiacol was observed compared with the original pill containing four crude drugs. It was clarified that the CUP2 prescribed in wood creosote pills induces the long MRT of guaiacol as a result of an increasing MDT. These results suggest that CUP2 might in part contribute to prolonged anti-diarrhea efficacy after oral administrations of wood creosote pills. Furthermore, these results are useful for the design of a new prescription of wood creosote pills and herbal drugs.

Acknowledgement

The authors wish to thank Ms. R. Hada (Osaka University of Pharmaceutical Sciences) for her technical assistance.

References and Footnotes


14) Although MRT values are not described in reference 8), we calculated it using the described data in reference 8).

**Japanese abstract**

4種の生薬（甘草、陳皮、黄柏、阿仙薬）を含む木クレオソート丸は、日本において療中毒、下痢の治療に用いられてきた。Guaiacolがその止瀉作用を担っていることはすでに明らかにされている。我々は木クレオソート丸に配合された生薬の薬剤学的役割を明らかにする研究に着手し、すでに陳皮（CUP2）がguaiacolの丸剤からの平均溶出時間（MDT）を遅延させることを報告した。

今回、4種薬を含む木クレオソート丸（P4R）とCUP2を含まない丸剤（P4R-CUP2）をラットに経口投与しguaiacolの血中動態に及ぼすCUP2の影響を検討した。その結果、P4R投与群のguaiacolの平均滯留時間（MRT）はP4R-CUP2に比べて有意に長かっただけで、両群の血中濃度時間曲線下面積（AUC_{0-24})には有意差が認められなかったので、guaiacolのMRTに対するCUP2の遅延効果は、平均溶出時間（MDT）の遅延によると考えられた。さらに、ひまし油で誘発した下痢病態においてもCUP2のMRTの遅延効果が認められた。MDTとMRTの遅延は薬物の持続効果の指標となることから、CUP2を木クレオソート丸の止瀉効果を持続させると考えられる。このような研究は伝統的な生薬配合剤の配合意義を解明するとともに、新たな配合剤を開発する指針になる。

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