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Anti-diarrheal effects of wood creosote pill preparation compounded with four crude drugs on castor oil-induced diarrhea in rats and the role of crude drugs in the expression of the efficacy

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Wood creosote pill preparation, in which 4 crude drug powders, Gambir, Phellodendri Cortex, Glycyrrhizae Radix, and Citri Unshiu Pericarpium are compounded, has been used for diarrhea. In the present study, the significance of the compounding of these crude drug powders was examined in castor oil-induced diarrhea model in rats.

Oral administration of small wood creosote pill (P4Rx5) exerted anti-diarrheal action for up to 3 hours and intestinal peristaltic motility-suppressive action, which was assessed by charcoal meal test. These suppressive actions were not noted in the groups of the rats receiving wood creosote alone at a dose level (11 mg/kg) that is contained in P4Rx5. From these findings, it was revealed that crude drugs compounded were responsible for the anti-diarrheal and intestinal peristaltic motility-suppressive actions of P4Rx5.

Pharmacological actions were examined for variant pills (without one of the crude drug powders), revealing that Citri Unshiu Pericarpium was responsible for retention of the anti-diarrheal effects and the suppression of castor oil-induced intestinal peristaltic motility by P4Rx5. Furthermore, it was found that the compounded crude drug powders increased the *AUC* of guaiacol (a major anti-diarrheal component of wood creosote), being involved in the intestinal peristaltic motility-suppressive action of P4Rx5. The results obtained in the present study may provide evidence supporting the usefulness of the compounding of the crude drugs in traditional wood creosote pills such as "Seiro-gan", and give a rationale for development of new preparations compounding wood creosote with crude drug powders.

Key words Wood creosote, guaiacol, castor oil-induced diarrhea, intestinal peristaltic motility, *Citrus unshiu.*

Abbreviations CUP, Citri Unshiu Pericarpium; CUP2, CUP preserved for 2 years; GAM, Gambir; PHC, Phellodendri Cortex; GLR, Glycyrrhizae Radix; WC, wood creosote;P4Rx5, wood creosote pill for rat containing four herbal drugs (5-fold higher than the common human clinical dose); P4Rx5-CUP2, P4Rx5 without CUP2; P4Rx5-GAM, P4Rx5 without GAM; P4Rx5-PHC, P4Rx5 without PHC; P4Rx5-GLR, P4Rx5 without GLR, P4Rx5-WC; P4Rx5 without WC; *MDT,* the mean dissolution time; *MRT,* the mean residence time; *AUC,* area under the concentration versus time curve; T_{max}, time to reach maximum plasma concentration; C_{max}, maximum plasma concentration.

Introduction

Wood creosote (beech wood creosote) is obtained by distillatory purification of wood tar obtained from beech and has been used as a gastrointestinal antiseptic.[1] It has been listed in the Japanese Pharmacopoeia from the First Edition (1886) as a therapeutic drug to treat diarrhea.[2] It has been known that wood creosote exerted anti-diarrheal action assessed by a castor oil-induced diarrhea model in rats[3] and that its major components (guaiacol and creosol) play a role in its pharmacological actions.[4]

In Japan, a wood creosote pill preparation (trade name: "Seiro-gan"), in which 4 crude drug powders are compounded, has been used for self-medication to treat diarrhea and abdominal pain. The regimen of the pill preparation is considered to be based on the preparations containing wood creosote and Glycyrrhizae Radix (GLR, Kanzo in Japanese) used in the Western countries.[2] However, no systematic studies on the significance of the compounding of other crude drugs such as Gambir (GAM, Asen'yaku in Japanese), Phellodendri Cortex (PHC, Obaku in Japanese) and Citri Unshiu Pericarpium (CUP, Chimpi in Japanese) have been made.

Therefore, we examined the significance of the compounding of the 4 crude drug powders, and found that CUP delayed the mean dissolution time (*MDT*)[5] and the mean residence time (*MRT*)[6] of guaiacol. In relation to this pharmaceutical study, in the present study we examined the role of the crude drug powders in anti-diarrheal action using a castor oil-induced diarrhea model in rats.

Materials and Methods

Materials. The same wood creosote (consisting of guaiacol, creosol and phenol at concentrations of 27.4 ±

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0.1, 19.5 ± 0.1 and 9.9 ± 0.1%, respectively), GAM, PHC, CUP and GLR as those used in the previous study[5] were used in the present study. CUP had been preserved for 2 years after harvest (CUP2), the botanical origin of which was presumed to be *Citrus unshiu* based on comparison with the HPLC profiles[7] reported previously. The voucher specimens of these crude drugs are deposited in the Research Institute of Taiko Pharmaceutical Co., Ltd.

Castor oil, loperamide hydrochloride, charcoal powder, and gum arabic were purchased from Maruzen Yakuhin Co., Ltd., Sigma Aldrich Japan Co., Ltd., Nacalai Tesque Inc., and Kanto Chemical Co., Ltd., respectively.

Preparation of pills. Using wood creosote and the 4 crude drug powders, pill preparations were prepared as reported[5] previously to obtain a small pill (P4Rx5) possible to be administered orally to rats. P4Rx5 (2.5 mm in diameter and 19 mg in weight containing 3.8 mg of wood creosote per pill) consists of the active ingredient corresponding to 5-fold of the clinical dosage. Five variant pill preparations shown in the legend of Fig. 1, in which wood creosote and 1 of the 4 crude drugs were deprived from P4Rx5, were prepared in the same manner.

Animal experiments. Ten-week old male Wistar ST rats were purchased from Japan SLC Inc., Hamamatsu, Japan, to use for this study, and they were kept for 14 days in an air-conditioned animal house with a diurnal light cycle and free access to diet and water. Rats with a body weight of 330 to 340 g were selected and used for this study. All animal experiments were carried out in compliance with the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Science.

Castor oil-induced diarrhea model. Diarrhea was induced on a group basis consisting of 10 rats after fasting for 18 hours with partial modification of the method reported by Niemegeers *et al.*[8] in the following manner. One hour after oral administration of castor oil (5.6 ml/kg) to the rats, pills were ejected into the stomach with 0.3 ml of purified water using a gastric sonde, on the tip of which the pills had been placed. The state of feces was checked twice 1 to 2 and 2 to 3 hours after administration of the respective pill preparations, and diarrhea was determined when the appearance of feces on the filter paper that had been laid beneath the animal cage was water-like to anidean. Purified water (0.3 ml)(control), wood creosote (11, 33 and 66 mg/kg) and loperamide hydrochloride (0.08 mg/kg) were also administered in the same manner.

Charcoal meal test. To clarify the mechanism of anti-diarrheal action of P4Rx5, intestinal peristaltic motility was assessed by charcoal meal test by partial modification of Green's method.[9] Namely, charcoal powder suspension (12 g of charcoal powder and 2 g of gum arabic in 100 ml of water) (2.3 ml/kg) was administered 2 hours after administration of the pill preparations to the rats treated with castor oil as described above, and 20 minutes thereafter the rats were killed. The ratio of the charcoal transit distance (position of charcoal powder) to the distance from the pylorus to the anal end of the ileum (total length of the small intestine) was determined as an index of intestinal peristaltic motility. A control group and groups receiving wood creosote and loperamide hydrochloride were also set in the same manner as in the diarrhea experiments.

Bioavailability of guaiacol. Bioavailability of guaiacol was determined as reported[6] previously. Namely, the rats were anesthetized with sodium pentobarbital (30 mg/kg) 1 hour after oral administration of castor oil (5.6 ml/kg), and then P4Rx5 was administered in the same manner as in the diarrhea experiments after inserting a cannula into the left jugular vein. Blood samples were collected *via* the cannula consecutively at 0, 5, 10, 20, 30, 60, 90, 120, and 180 minutes after P4Rx5 administration, and the plasma fraction was immediately separated from the heparinized blood samples by centrifugation and stored at -20℃. Plasma guaiacol concentrations were determined after treating the plasma samples with *Helix pomatia* sulfatase (1.8 units/μl, EC3.1.6.1, type H-1 with β-glucuronidase activity; Sigma-Aldrich, Japan) by the GC/MS method as reported[6] previously.

Quantitative analysis of plasma guaiacol by GC/MS: GC(Shimadzu GC-17A): column, BPX5 25 m x 0.22 mm i.d.; column temp, 50℃ (1 min) -10℃ /min-200℃ (2 min); injection temp, 250℃; carrier gas, helium (70 kPa); injection mode, splitless. MS (Shimadzu QP5050A): EI (70 eV), SIM (*m/z* 112: 2-fluorophenol, *m/z* 124: guaiacol).

The maximum plasma concentration (C_{max}) and the time to attain C_{max} (T_{max}) of guaiacol were determined directly from the actual plasma concentrations. The area under the curve of mean plasma concentration versus time from 0 to 3 hours ($AUC_{0\text{-}3h}$) was calculated using the WinNonlin™ software (Pharsight Corp., USA). Wood creosote (11, 33 and 66 mg/kg) was also administered in the same manner.

Statistics. The data obtained in the present study were represented as the mean ± S.D., and compared using the Student's *t*-test and the Fisher's exact test. Significance level was set as being $p<0.05$.

Results

Anti-diarrheal effects (Fig. 1). Diarrhea was induced in all the control rats receiving purified water alone 1 to 3 hours after castor oil administration. As shown in the left panel in Fig.1, diarrhea was significantly suppressed in the group receiving P4Rx5 compounded with the 4 crude drugs 1 to 2 hours after oral administration. Diarrhea was not suppressed in the group receiving wood creosote alone at a dose level (11 mg/kg) that is contained in P4Rx5, although anti-diarrheal effects were noted in the groups receiving wood creosote alone (33 and 66 mg/kg). Also, diarrhea was not suppressed in the group receiving the variant pill preparation deprived of wood creosote (P4Rx5-WC). Diarrhea was significantly suppressed in the groups receiving any of the 4 variant pill preparations deprived of 1 of the 4 crude drugs, but a decreasing trend in the rate of diarrhea suppression was found in these groups compared to that of the group receiving the original pill preparation (P4Rx5).

As shown in the right panel of Fig.1, similar anti-diarrheal effects were found in all the groups 2 to 3 hours

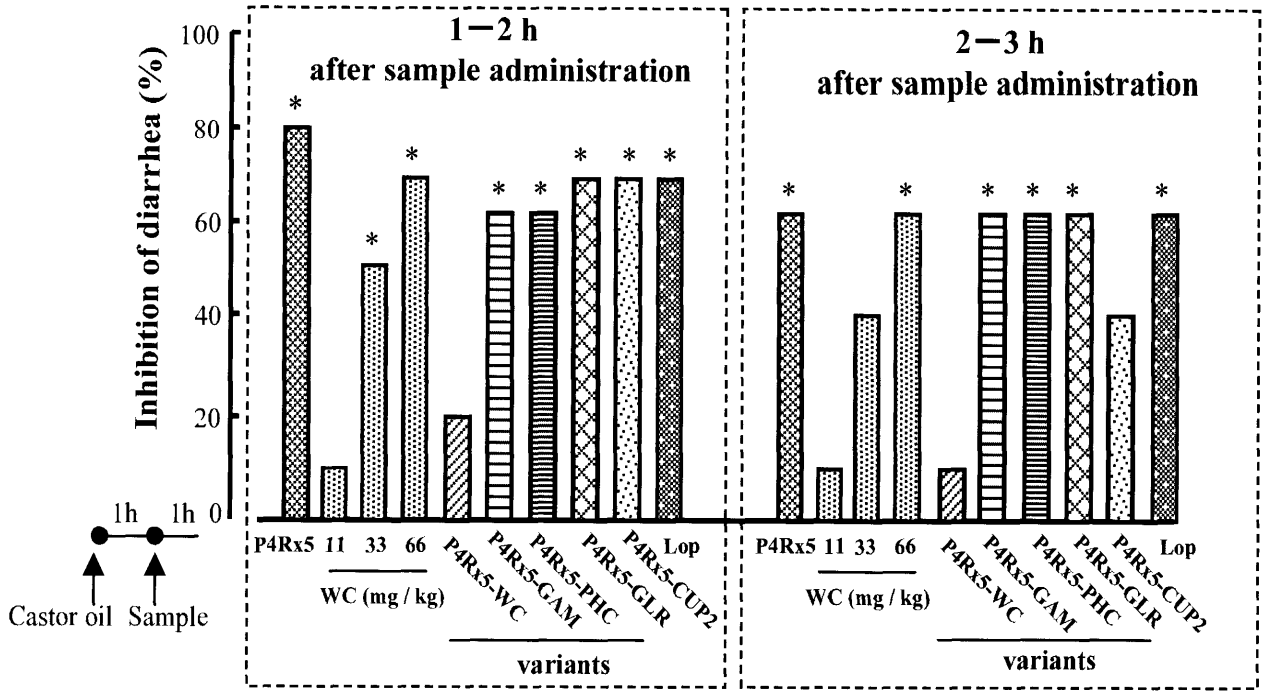

Fig. 1 Anti-diarrheal effects of pills and wood creosote on castor oil-induced diarrhea in rats.
Inhibition of diarrhea represents as (10-number of diarrhea rats)x100/10 (%).
*$p<0.05$ *vs* control (by Fisher's exact test).
P4Rx5 contains WC (3.8 mg/pill), GAM (1.9 mg/pill), PHC (2.8 mg/pill), GLR (1.4 mg/pill), CUP2 (2.8 mg/pill) and glycerin(0.9 mg/pill) (5-fold higher than the common human clinical dosage); P4Rx5-GAM: P4Rx5 without GAM; P4Rx5-PHC: P4Rx5 without PHC; P4Rx5-GLR:P4Rx5 without GLR; P4Rx5-CUP2: P4Rx5 without CUP2; P4Rx5-WC: P4Rx5 without WC; WC: wood creosote; Lop: loperamide hydrochloride (0.08 mg/kg; 5-fold higher than the common human clinical dose).

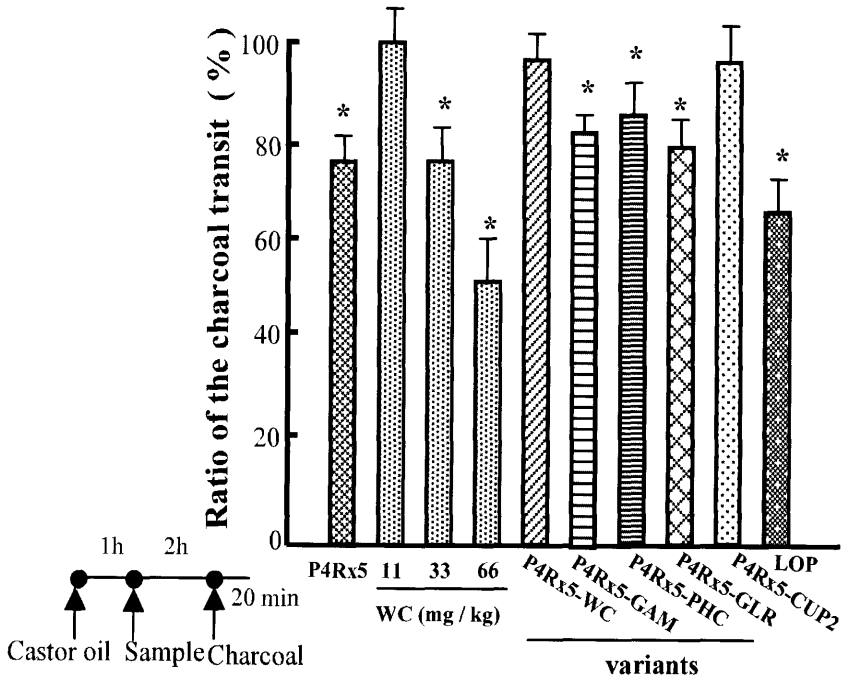

Fig. 2 Effects of pills and wood creosote on the ratio of the charcoal transit in the intestine in castor oil-induced diarrhea in rats.
One hour after administration of castor oil, pills and wood creosote were administered. After 2 hr, a charcoal meal was administered and its proportion of the small intestinal transit was measured after 20 min. Each value represents the percentage of control (mean±S.D., n= 4).
*$p < 0.05$ *vs* control.
Abbreviations are shown in the legend of Fig.1

after administration of the pill preparations except for P4Rx5-CUP2.

Suppression of intestinal peristaltic motility (Fig. 2). As shown in Fig.2, intestinal peristaltic motility that was assessed based on charcoal transit in intestine was significantly suppressed by administration of P4Rx5 (76.6±4.0%; n=4). Although a dose dependent and significant suppression of charcoal transit was found in the groups receiving wood creosote alone (33 and 66 mg/kg), no suppression was found in the group receiving wood creosote alone at a dose level (11 mg/kg) that is contained in P4Rx5.

Furthermore, although no suppression of charcoal transit

was noted in the groups receiving the variant pill preparations (P4Rx5-WC or P4Rx5-CUP2) in which wood creosote or CUP2 is deprived from P4Rx5, respectively, a significant suppression was noted in the groups receiving any of the other 3 variant pill preparations (P4Rx5-GAM, P4Rx5-PHC, or P4Rx5-GLR).

Bioavailability of guaiacol (Fig. 3 and Table 1). The time courses of the change in plasma levels of guaiacol and its pharmacokinetic parameters after administration of P4Rx5 or wood creosote in the castor oil-induced diarrhea of rats are shown in Fig. 3 and Table 1, respectively. The T_{max} of guaiacol in the groups receiving P4Rx5 (0.9±0.2 h) was significantly longer than that of the groups receiving wood creosote alone (at the 3 doses), and the C_{max} and the plasma guaiacol levels at 1, 1.5, and 2 hours after administration were significantly higher in the groups receiving P4Rx5 than those in the groups receiving wood creosote alone (at a dose of 11 mg/kg). Furthermore, the $AUC_{0\text{-}3h}$ of guaiacol (16.1 ± 2.3 μg · h/ml) in the groups receiving P4Rx5 was significantly greater than that of the groups receiving the same dose of wood creosote alone (11 mg/kg) (4.2±0.5 μg · h/ml), and it was almost the same as that of the group receiving wood creosote at a dose of 33 mg/kg. The *MRT* of guaiacol (1.3±0.0 h) in the groups receiving P4Rx5 was significantly longer than that of the groups receiving wood creosote alone at the same dose (11 mg/kg) (0.7±0.1 h).

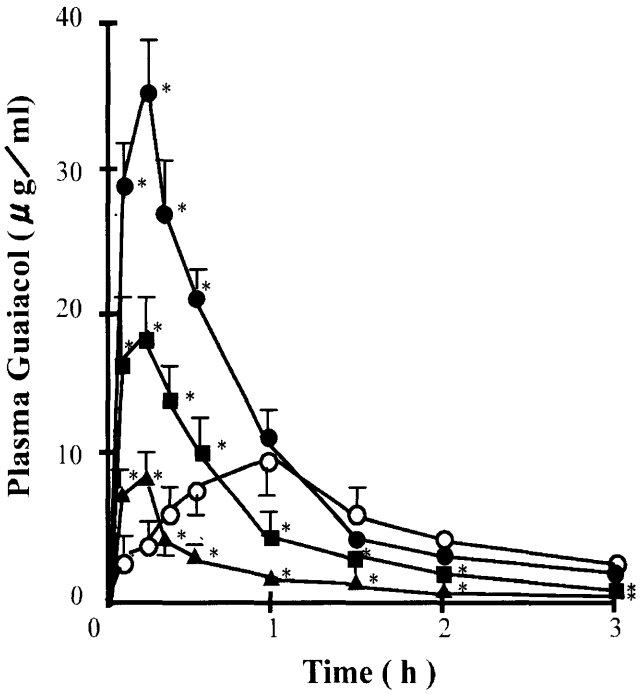

Fig. 3 Plasma guaiacol concentration after oral administration of pill and wood creosote on castor oil- induced diarrhea in rats
Each total (conjugated and unconjugated) guaiacol concentration represents the mean±S.D.(n=6). The total concentration (unconjugated and conjugated: glucuronide and sulfate forms) was measured as the plasma guaiacol concentration. ○: P4Rx5; ▲: wood creosote (11 mg/kg);. ■: wood creosote (33 mg/kg); ●: wood creosote (66 mg/kg);
Composition of P4Rx5 is shown in the legend of Fig.1.
*$p < 0.05$ *vs* P4Rx5.

Discussion

The major indication of the wood creosote pill preparation containing the 4 crude drug powders (trade name: Seiro-gan) used for self-medication in Japan is diarrhea. The anti-diarrheal effects of wood creosote alone have been proved using a castor oil-induced diarrhea model of rats (ED_{50}: 53 mg/kg).[3] In addition, guaiacol and creosol have been reported to be the anti-diarrheal components of wood creosote.[4] However, involvement of the 4 crude drug powders (GAM, PHC, GLR and CUP2) that are compounded in the wood creosote pill preparation in anti-diarrheal effects has not been clarified. In the present study, pill preparations for rats (P4Rx5: 3.8 mg of wood creosote/pill) containing the 4 crude drug powders were prepared, and the pharmacological significance of the compounding of these crude drugs was investigated using the castor oil-induced diarrhea model in rats.

As a result, it was confirmed that significant anti-diarrheal effects were noted for up to 3 hours after oral administration of P4Rx5 (Fig.1). No anti-diarrheal effects were noted for the variant pill preparations deprived of wood creosote from P4Rx5 (P4Rx5-WC), clearly indicating that wood creosote plays a role in the anti-diarrheal action of P4Rx5. It is particularly notable that no anti-diarrheal effects were noted in the groups receiving wood creosote alone at the same dose (11 mg/kg) as that contained in P4Rx5. This suggests that the 4 crude drug powders compounded in P4Rx5 may be responsible for the anti-diarrheal action of P4Rx5.

Next, 4 variant pill preparations in which one of the 4 crude drug powders was deprived from P4Rx5 were prepared, and similar experiments were carried out to examine the effects of the respective crude drug powders on anti-

Table 1 Pharmacokinetic parameters of guaiacol from pill and wood creosote in rats

	T_{max} (h)	C_{max} (μg/ml)	$AUC_{0\text{-}3h}$ (μg.h/ml)	*MRT* (h)
P4Rx5 (11 mg/kg)	0.9 ± 0.2	9.8 ± 1.8	16.1 ± 2.3	1.3 ± 0.0
WC (11 mg/kg)	0.2 ± 0.0*	7.7 ± 0.7*	4.2 ± 0.5*	0.7 ± 0.1*
WC (33 mg/kg)	0.1 ± 0.0*	19.6 ± 3.3*	15.0 ± 2.2	0.8 ± 0.1*
WC (66 mg/kg)	0.2 ± 0.0*	36.7 ± 2.5*	29.3 ± 2.0*	0.7 ± 0.0*

Each value represents the mean ± S.D. (n=6). *:$p<0.05$ *vs* P4Rx5.
T_{max}: time required to reach C_{max}. C_{max}: maximum plasma concentration. $AUC_{0\text{-}3h}$: area under the plasma concentration curves from zero to 3h. *MRT*: mean residence time. WC: wood creosote.
Composition of P4Rx5 is shown in the legend of Fig.1.

diarrheal action. This led to the finding that the anti-diarrheal effects of P4Rx5-CUP2 disappeared within 2 to 3 hours after administration, suggesting that CUP2 might be involved in the retention of the anti-diarrheal action. This finding is correlated with the data that CUP2 delayed the mean residence time (*MRT*) of guaiacol.[6] *MRT* is one of the important pharmacokinetic parameters relevant to retention of a pharmacological action.[10]

Because anti-diarrheal effects similar to those of P4Rx5 were found for any other 3 variant pill preparations up to 3 hours after administration, involvement of GAM, PHC and GLR in the anti-diarrheal effects were considered to be less likely than that of CUP2. In addition, it has been revealed that castor oil-induced diarrhea in mice is suppressed by administration of berberine (7.5 mg/kg[11] and 10 mg/kg).[12] In the present experiments, the dose of berberine (0.19 mg/kg in rats), an ingredient of Phellodendri Cortex (PHC), in the groups receiving P4Rx5 was considered insufficient to exert anti-diarrheal effects, in addition to the potential species difference between rat and mouse.

Castor oil is converted to recinoleic acid in the small intestine, which is considered to induce inflammatory diarrhea *via* enhancement in intestinal peristaltic motility.[13] From the results of the charcoal meal test shown in Fig. 2, it was concluded that wood creosote suppressed intestinal peristaltic motility (that is charcoal transit). These results were in agreement with the previous data,[3] as well as the report on the suppression of colonic bead expulsion by wood creosote, which has been known to be involved in the anti-diarrheal action of wood creosote.[14]

Furthermore, suppression of charcoal transit by P4Rx5 was found in the present study, while these effects were not noted in the groups receiving wood creosote alone at the same dose level (11 mg/kg) as that contained in P4Rx5, suggesting that the crude drugs compounded in P4Rx5 might be involved in the intestinal peristaltic motility-suppressive action of P4Rx5. Among the findings of the present study, disappearance of the charcoal transit suppression in the groups receiving P4Rx5-CUP2 suggested that CUP2 might be involved in the suppression of castor oil-induced intestinal peristaltic motility. In addition, sustained suppression of intestinal peristaltic motility was noted in the groups receiving variant pill preparations deprived of PHC containing berberine that is reported to suppress intestinal peristaltic motility at dose 10 mg/kg.[15] However, the present dose of berberine (0.19 mg/kg) in the groups receiving P4Rx5 was lower than that reported, therefore it was unlikely that berberine was involved in the suppression of intestinal peristaltic motility in the present study. Further investigations are necessary to elucidate the mechanisms by which P4Rx5 and crude drugs compounded suppressed diarrhea and intestinal peristaltic motility induced by castor oil.

Because wood creosote has been known to suppress intestinal peristaltic motility *via* the blood,[14] we investigated the plasma pharmacokinetics of guaiacol that is an active component exerting the pharmacological action of wood creosote after P4Rx5 administration. As shown in Fig.3 and Table 1, T_{max} of guaiacol of the groups receiving P4Rx5 is significantly longer than that of the groups receiving wood creosote alone. These results suggest that T_{max} of guaiacol depends on crude drugs compounded in pills, which is similar to those in our previous report.[5] We have already demonstrated that, among the crude drug powders compounded in wood creosote pill preparation, CUP2 increased the *AUC*[6] and delayed the *MDT*[5] of guaiacol. $AUC_{0\text{-}3h}$ of guaiacol in the groups receiving P4Rx5 was found to be significantly greater than that of the groups receiving wood creosote alone (at a dose of 11 mg/kg). The increase in *AUC* of guaiacol has been considered due to increase in absorption in the digestive canal and to decrease metabolism in the digestive canal and liver by crude drugs compounded in pills, and details of participation of crude drugs are the subject for a future study.

In summary, the main findings of the present study were that the crude drug powders compounded in P4Rx5 were involved in both retention and enhancement of the anti-diarrheal action of wood creosote. The present study revealed that, among the 4 crude drug powders, Citri Unshiu Pericarpium was involved in retention of the anti-diarrheal action of the original P4Rx5, and also in suppression of the castor oil-induced intestinal peristaltic motility. Furthermore, the present study also revealed that the crude drug powders compounded in P4Rx5 increased the *AUC* of guaiacol (a major anti-diarrheal component of wood creosote), and that they were involved in suppression of intestinal peristaltic motility. The findings of the present study may give a rationale for the currently used regimen of traditional wood creosote pills such as "Seiro-gan", and provide important guidelines for designing new combinations of wood creosote and crude drugs.

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Japanese abstract

4種類の生薬末（阿仙薬，黄柏，甘草，陳皮）を配合したwood creosote丸剤は下痢の治療薬として古くから用いられている。この報告ではこれら生薬末の配合意義をcastor oil処理したラットを用いて検討した。

ラットに経口投与できる大きさに調製したwood creosote丸剤（P4Rx5）は投与3時間後まで有意な止瀉作用を示し腸蠕動運動も抑制した。この止瀉作用と腸蠕動運動抑制作用は，P4Rx5と同量のwood creosote（11 mg/kg）を単独で投与した群では認められなかった。これらのことからP4Rx5に配合されている4生薬末がこれらの抑制作用に関与していることが明らかになった。次にP4Rx5から1生薬末を抜いた丸剤で同様の検討を行った結果，陳皮末（CUP2）が元のP4Rx5の止瀉作用の持続性を高め，さらに腸蠕動運動の抑制に寄与していることが明らかになった。

さらに配合された生薬末はguaiacol（wood creosoteの主要な止瀉成分）のAUCを増加させ，P4Rx5の腸蠕動運動の抑制作用に寄与していることが明らかになった。今回の結果は4種類の生薬末を配合したwood creosote丸剤（伝統薬：正露丸）における配合生薬の意味を解析し有用性を支持する証拠となる。このような評価方法はwood creosote丸製剤の配合生薬を改変する指標となる。

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