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RESEARCH ARTICLE

Effect of the *Phragmitis rhizoma* Aqueous Extract on the Pharmacokinetics of Docetaxel in Rats

Sarah Shin[1], No Soo Kim[1], Young Ah Kim[1], Hea Ry Oh[1] and Ok-Sun Bang[1,*]

[1]*Clinical Medicine Division, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea*

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Abstract: ***Background*:** Traditionally, *Phragmitis rhizoma* has been prescribed to relive a fever, vomiting, dysuria, and constipation, and to promote secretion of fluids. In addition, recent studies have reported its efficacy as a diuretic and antiemetic. Our previous study demonstrated that the *Phragmitis rhizoma* aqueous extract (EPR) ameliorates docetaxel (DTX)-induced myelotoxicity. ***Aim and Objective*:** This study was aimed to investigate the effects of EPR on the pharmacokinetics of DTX in Sprague–Dawley rats.

***Materials and Methods*:** The animals received an intravenous injection of DTX (5 mg/kg) with or without oral EPR (100 mg/kg) pretreatment for 1 or 6 days. The pharmacokinetics of plasma DTX was analyzed using an ultra-performance liquid chromatography-tandem mass spectrometry system, and pharmacokinetic parameters were estimated *via* noncompartmental analysis.

***Results*:** Relative to the control group (DTX alone), EPR pretreatment did not affect significantly the overall profiles of plasma DTX levels. Consecutively pretreated EPR for 6 days slightly altered $AUC_{0\text{-}t}$ and C_{max} of DTX by 122 and 145.9%, respectively, but these data did not reach the threshold of statistical significance ($p > 0.05$).

***Conclusion*:** These results indicate that DTX exposure may not be affected by EPR treatment at the dose level used in this study, suggesting that oral EPR can be used safely when taken with intravenously injected DTX. However, further studies under the stringent conditions are needed when chronic treatment of EPR and anticancer drug.

Keywords: *Phragmitis rhizoma*, Docetaxel, pharmacokinetics, herb-drug interaction, anticancer drug, chemotherapy.

1. INTRODUCTION

Docetaxel (DTX; brand name Taxotere®) is a type of taxoid anticancer agent. Clinically, it is widely used to treat various malignant solid tumors including breast, prostate, ovarian, and lung tumors [1]. Unfortunately, DTX has diverse adverse side effects such as severe vomiting, extreme weakness, fever, nourishing, hair loss, neuropathies, and myelotoxicity [2]. In the past, cancer research has focused on curing cancer itself. At present, the emphasis has additionally been placed on improving the quality of life by alleviating the side effects of chemotherapy [3]. Complementary and alternative medicine has been used globally to manage the adverse effects and improve the overall efficacies of chemotherapy [3].

Phragmitis rhizoma is the dried root stock of *Phragmites communis* Trinius, a perennial herbaceous plant that grows natively in the Northern Hemisphere [4]. It has been prescribed in traditional Korean and Chinese medicine to relieve fever, vomiting, dysuria, and constipation [4-6]. Our previous study illustrated that the *Phragmitis rhizoma* aqueous extract (EPR) and its major component, *p*-hydroxycinnamic acid (HCA) significantly ameliorates DTX-induced myelotoxicity both *in vitro* and *in vivo* [7]. Therefore, EPR can be considered an effective complementary remedy for patients who suffer from chemotherapy-induced myelotoxicity.

One research demonstrated that the pharmacokinetic profiles and bioavailability of drugs can be affected by co-administered of herbal extracts or their phytochemical compounds though modulating the activity or expression of drug-metabolizing enzymes and/or membrane transporters to regulate the absorption and secretion of drugs [8]. Therefore, when herbal medicines are used to relieve the adverse effects of conventional therapy, the possibility of herb-drug interactions should be carefully investigated to ensure the safe use of herbal medicines as complementary medicine. The present study investigated the herb-drug interactions between DTX and EPR by determining the pharmacokinetic profiles of DTX in the plasma of rats with or without oral EPR pretreatment.

*Address correspondence to this author at the Clinical Medicine Division, Korea Institute of Oriental Medicine, 1672 Yuseong-daero, Yuseong-gu, Daejeon 34054, Republic of Korea; Tel: +82-42-868-9353;
E-mail: osbang@kiom.re.kr

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2. MATERIALS AND METHODS

2.1. Chemicals

All chemicals (purity ≥ 99.0%) used for the animal study and *p*-HCA (purity ≥ 98.0%) as a standard chemical for a chromatographic analysis were purchased from Sigma-Aldrich. Ultra-performance liquid chromatography (UPLC)-grade solvents (purity ≥ 99.8%) including water, acetonitrile, and methanol were purchased from Fisher Scientific Ltd. (Loughborough, UK).

2.2. Plant Materials

Phragmitis rhizoma was supplied by Kwangmyungdang Medicinal Herbs Co. (Ulsan, Republic of Korea) and identified by Dr. Goya Choi (Herbal Medicine Research Center, Korea Institute of Oriental Medicine, KIOM). A voucher specimen (KIOM-CRC#172) was stored in the Clinical Medicine Division, KIOM, Republic of Korea.

2.3. Extract Preparation and Chromatographic Analysis

Extraction and chromatographic analysis of *Phragmitis rhizoma* was conducted as previously described [7]. Briefly, for preparation of EPR, dried *Phragmitis rhizoma* (300 g) was finely ground and refluxed in water twice for 2 h each, and then the extracts were filtered through cotton wools. The filtrates were further concentrated and dried using a spray dryer (IlShin Biobase). The final extracts (EPR, 36 g, 12%) were homogenized and stored at 4°C in a dark, airtight container under a desiccated condition. The EPR was clearly dissolved in pure distilled water at 10 mg/mL.

Fingerprinting analysis of the EPR was performed with the 1290 infinity UPLC system (Agilent Technologies) equipped with an analytical column (Kinetex XB-C18). The EPR and *p*-HCA were dissolved at 10 and 0.1 mg/mL in 50% (v/v) aqueous methanol solution, respectively. The detailed conditions for UPLC analysis are summarized in Table **1**.

2.4. Animals

All procedures for the animal study were reviewed and approved by the Institutional Animal Care and Use Committee of the KIOM (protocol number #17-087). Male Sprague–Dawley rats (6 weeks old, 180-190 g) were supplied by OrientBio Inc. (Seongnam, Republic of Korea) and acclimated for 1 week before experimentation in a specific-pathogen-free facility under controlled conditions (temperature, 22-24°C; humidity, 50-60%; 12 h/12 h light–dark cycle).

2.5. Drug Treatments

Rats were randomly divided into three groups as follows: group 1, control, intravenous (i.v.) bolus injection of 5 mg/kg DTX; group 2, single oral administration of EPR; and group 3, oral administration of EPR for 6 consecutive days. The rats in groups 2 and 3 received the DTX injection 0.5 h after oral EPR dose (100 mg/kg). As previously reported, the DTX stock solution was prepared at 25 mg/mL in polysorbate 80: ethanol (1:1, v/v) and then diluted to a 2.5 mg/mL using a physiological saline solution for preparation of clear and stable solution without aggregation, immediately before administration *via* tail vein injections [9, 10].

2.6. Pharmacokinetic Study

To evaluate the pharmacokinetics of DTX in with or without EPR pretreatment**,** the rats in groups 2 and 3 received EPR before the DTX injection as described previously. At 0.083 (5 min), 0.25, 0.5, 1, 4, 8, and 24 h after the DTX injection, whole blood (0.25 mL) was collected from the external jugular vein into K_2EDTA-coated tubes and centrifuged at 5,000 *g* for 5 min at 4°C to obtain plasma, which was mixed with methanol (1 mL) and vortexed for 5 min. The mixture was centrifuged at 3,000 × *g* for 5 min to remove endogenous proteins. The residual supernatant was completely evaporated using a Savant Speed-Vac (Thermo Fisher Scientific, Inc.). The dried precipitate was re-dissolved in 0.1 mL of a blended solution (50% methanol in water), after which a 5 μL sample was analyzed using a UPLC-tandem mass spectrometry (MS/MS) system. The plasma levels of DTX were determined *via* a modified liquid chromatography-MS/MS method as previously described [9, 11] using a Xevo TQ-S system (Waters) in the positive ion mode equipped with an ACQUITY UPLC system (Waters). The plasma samples were separated on a reverse phase C8-column (Phenomenex Kinetex, 2.1 × 50 mm, 2.6 μm) at 30°C. Analytes were eluted under an isocratic condition (40:60 mixture) for 5 min followed by a sequential gradient (from

Table 1. The detailed chromatographic condition for qualitative and quantitative analysis of EPR.

Chromatographic Parameter		Condition	
Instrument		1290 infinity UHPLC system (Agilent)	
Column		Kinetex XB-C18 (2.1*50 mm, 1.7 μm, Phenomenex)	
Temperature of column oven		30°C	
Temperature of auto-sampler		4°C	
Detection		DAD at 310 nm	
Injection volume		2 μL	
Flow rate		0.3 mL/min	
Mobile phase	**Time (min)**	**% of A (0.1% Formic acid in water)**	**% of B (Acetonitrile)**
	0	99	1
	40	55	45

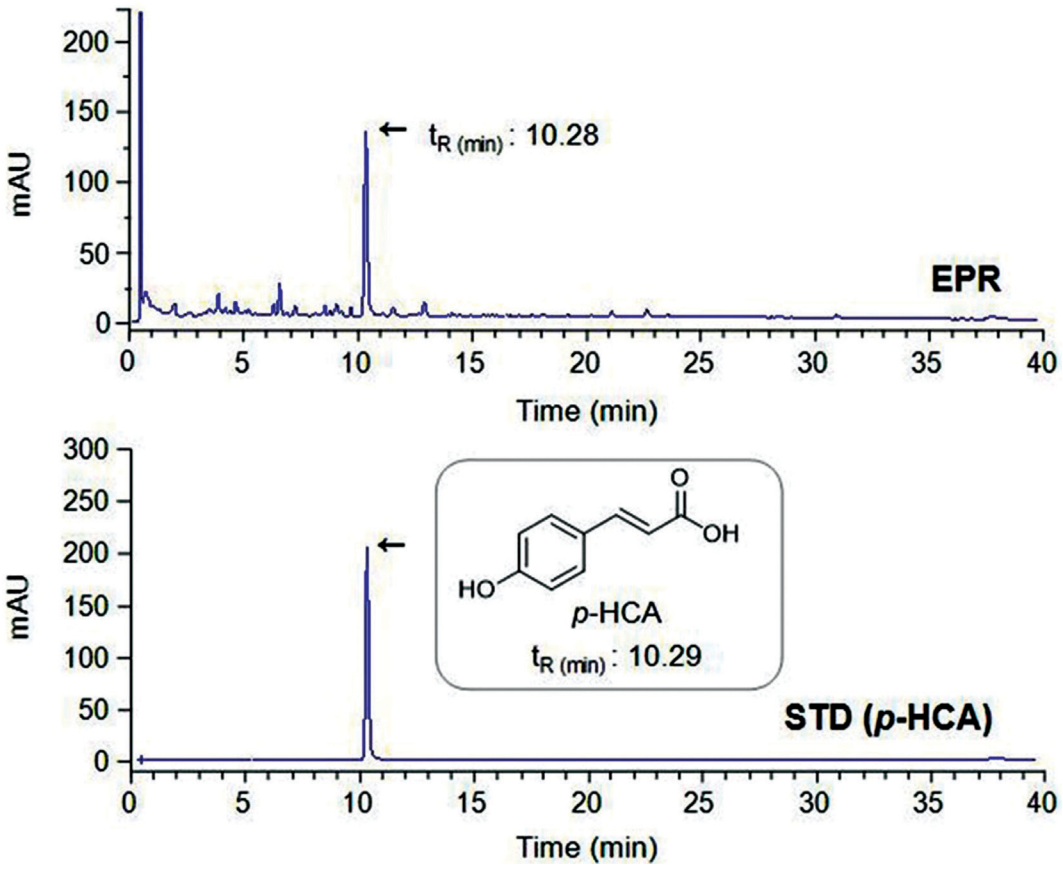

Fig. (1). Chromatographic fingerprinting analysis of the EPR. UPLC analysis was performed on the EPR and *p*-HCA. The chromatograms of the EPR (upper panel) and a reference standard *p*-HCA (lower panel) were monitored using a UV at 310 nm.

40:60 to 1:99) of water-acetonitrile containing 0.1% (v/v) formic acid over 5 min at a flow rate of 0.3 mL/min. Mass analysis was conducted in the multiple reaction monitoring (MRM) mode. The precursor–product pair of DTX used for MRM was 830.14-549.21 m/z. For assay quality control, the linearity was confirmed over the range of 0.01-1,000 ng/mL with a correlation of determination of 0.998. The signal-to-noise ratio exceeded 80-fold at the lowest concentration of the assay range. The precision coefficient variation was less than 10%. The percent recoveries were more than 85% in low, medium, and high concentration of analysts. The pharmacokinetic parameters of DTX were automatically calculated using a noncompartmental model by PK Solver (ver. 2.0, add-in program in Microsoft Excel).

2.7. Statistical Analysis

All data are presented as the mean ± SD. The means were compared using one-way analysis of variance (ANOVA) followed by the Dunnett *post-hoc* test for parametric values or Kruskal–Wallis one-way ANOVA on ranks for nonparametric values. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS AND DISCUSSION

The EPR was prepared as previously described [7] and a goldish yellow powder was obtained with 12% yields. To confirm the quality and quantity of prepared EPR, its fingerprinting analysis of EPR was performed using a UPLC system with the condition as summarized in Table **1**. The representative UPLC chromatograms of the EPR and a reference standard chemical *p*-HCA with its chemical structure were compared as shown (Fig. **1**). The time of retention (t_R) and specific UV absorption spectra of the major peak in EPR (t_R of peak =10.28 min, upper panel) and *p*-HCA (t_R of peak =10.29 min, lower panel) were perfectly matched in this chromatograms. Therefore, the chromatographic data assess that the major peak observed in the EPR chromatogram is *p*-HCA and it accounted for 36% of peak area detected UV at 310 nm and was measured at 0.64 ± 0.03 mg of *p*-HCA per 1 g of EPR. In addition, recent researches also revealed that *p*-HCA is a major component isolated from the *Phragmitis rhizome* [7-8, 12].

To validate the accuracy of analytical method for detection and recovery of DTX in plasma, we first confirmed the DTX peak in blank plasma, in the standard DTX solution, plasma spiked with DTX, and analytic plasma samples using a UPLC-MS/MS analysis system. In this system, we first validated that interfering peak with DTX was not observed in blank plasma (Fig. **2A**), and then confirmed that the clear DTX peak detected in the standard solution (Fig. **2B**) was also observed in both DTX-spiked blank plasma (Fig. **2C**) and the analytic plasma sample from DTX-administered rats (Fig. **2D**). The data indicate that DTX concentrations in plasma can be precisely determined using this analysis system after an i.v. injection of 5 mg/kg DTX to rat without any interference between endogenous substances in plasma and DTX. Next, we analyzed the level of DTX in plasma at regular time points using a validated

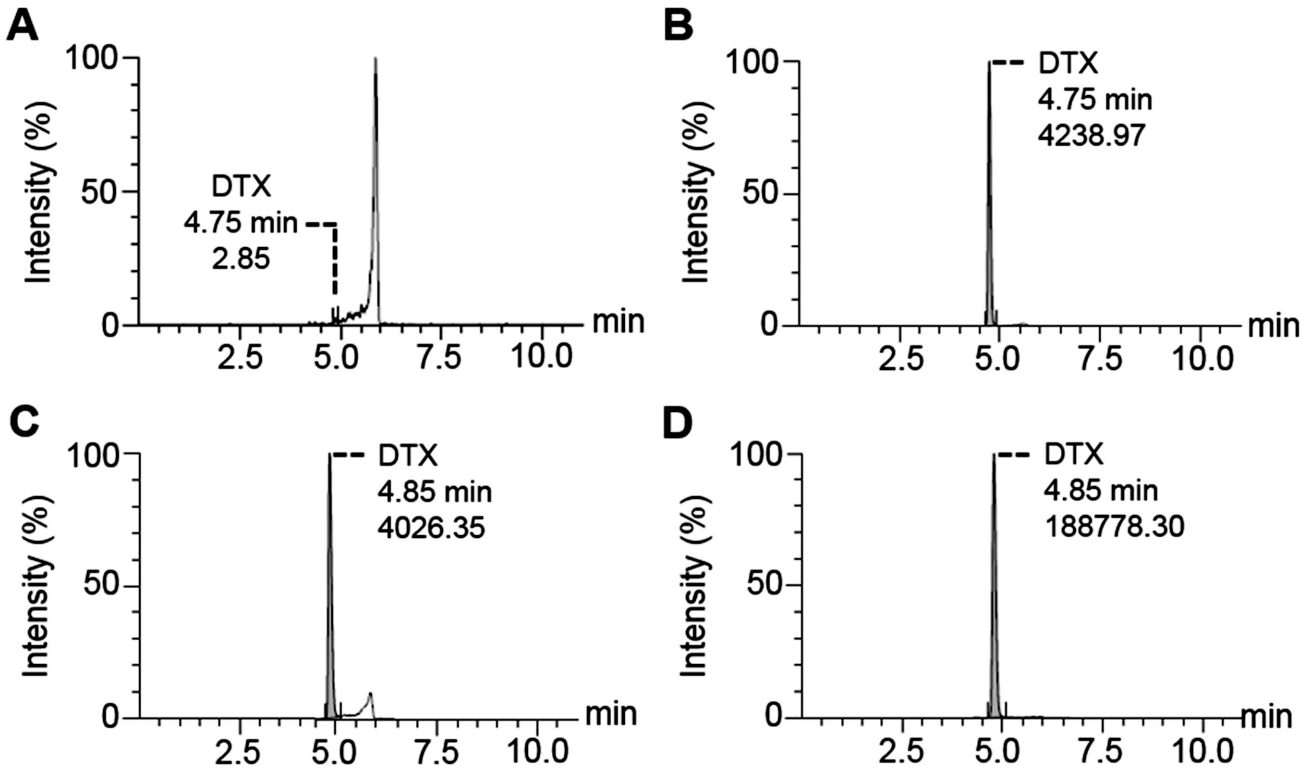

Fig. (2). Representative MRM chromatograms of DTX. (**A**) Blank plasma, (**B**) standard DTX solution, (**C**) blank plasma spiked with DTX, and (**D**) plasma sample that was obtained 5 min after i.v. injection of 5 mg/kg DTX in rats.

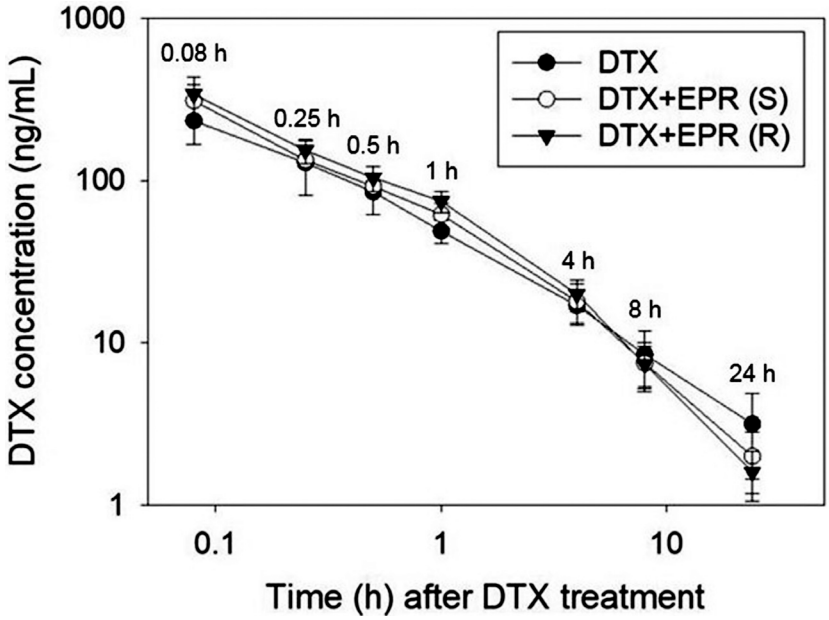

Fig. (3). Mean plasma concentrations of DTX following i.v. injection of 5 mg/kg DTX with or without EPR pretreatments (oral administration of 100 mg/kg EPR for 1 or 6 consecutive days). EPR (S) and EPR (R) indicate EPR treatment for 1 and 6 consecutive days before DTX injection, respectively. Data are presented as the mean ± SD for each group (n = 4–6).

UPLC-MS/MS method after DTX i.v. injected to rat with or without EPR pretreatment. The ranges of blood collection time point for i.v. DTX was already shown in various papers. Most of that adopted time range of 0.083 h (5 min) to 24 h and 7~10 time points for pharmacokinetic evaluation of DTX as usually adopted in a few studies [9, 12, 13]. We administered DTX to rat with 5 mg/kg as the reported dose in general pharmacokinetic experiments of DTX [11]. The dosage of EPR was chosen at 100 mg/kg, based on our previous *in vitro* and *in vivo* myelosuppression efficacy test showing the mean ameliorating effect of DTX induced myelotoxicity [7]. To avoid incidental interference by a combination with medication and medicinal herbal extract, EPR was orally treated 0.5 h prior to i.v. DTX [10, 12, 14-17]. Applying these several factors, we evaluated the pharmacokinetics of DTX following i.v. administration in rats 0.5 h after oral pretreatment with EPR for 1 or 6 consecutive days.

As shown in (Fig. **3**), the overall profiles of the mean plasma DTX concentrations versus time curves were similar regardless of EPR pretreatment. The pharmacokinetic parameters of DTX are summarized in Table **2**. EPR pretreatment did not induce any significant alterations of area under the plasma concentration versus time curve (AUC_{0-t}) (from 356.62 ± 41.06 to 382.72 ± 60.73 [p = 0.44] for single treatment, and to 435.23 ± 85.7 ng*h/mL [p = 0.08] for repeated treatment) and the maximal plasma concentration (C_{max}) (from 233.83 ± 66.63 to 310.50 ± 76.95 [p = 0.13] for single treatment, and to 341.20 ± 91.64 ng/mL [p = 0.05] for repeated treatment). Nonsignificant alterations were also observed for half-life ($t_{1/2}$) (from 7.07 ± 1.95 to 6.33 ± 1.92 [p = 0.57] for a single treatment and to 5.31 ± 1.12 h [p = 0.11] for repeated treatment) of DTX. In addition, other pharmacokinetic parameters such as the terminal elimination rate constant and time to reach C_{max} (t_{max}) were not changed by EPR pretreatment. It has been shown that overall plasma concentration of the drug is a good predictor of its systemic exposure in the efficacy and toxicity experiments [18]. In the present study, the data indicated that EPR pretreatment does not significantly affect systemic exposure of DTX, as shown in its pharmacokinetic profiles in plasma.

Table 2. Pharmacokinetic parameters of DTX in plasma following the i.v. injection of 5 mg/kg DTX in rats with or without the EPR pretreatment for 1 or 6 consecutive days.

Parameter (unit)	Control	Oral pretreatment (100 mg/kg EPR)	
		Single Dose	Consecutive Dose
C_{max} (ng/mL)	233.83 ± 66.63	310.50 ± 76.93	341.20 ± 91.64
AUC_{0-t} (ng*h /mL)	356.62 ± 41.06	382.72 ± 60.73	435.23 ± 85.70
$t_{1/2}$ (h)	7.07 ± 1.95	6.33 ± 1.92	5.31 ± 1.12
λ_z (/h)	0.11 ± 0.03	0.12 ± 0.03	0.13 ± 0.03

Data are presented as the mean ± SD for each group (n = 4–6).

The pharmacokinetic profile of an anticancer drug can be modulated by the herb-drug interactions, which involve phase I/II metabolic enzymes, transmembrane transporters, or other environmental factors [8]. In particular, DTX is mainly metabolized in the liver by cytochrome P450 (CYP) enzymes, especially CYP3A4 [10, 19]. Effect of EPR on metabolizing enzymes of DTX is helpful to predict adverse effects due to undesirable herb-drug interactions. Our previous *in vitro* study illustrated that the *in vitro* inhibitory effects of EPR and its major component, *p*-HCA on human CYPs were mostly minimal (unpublished data). Moreover, we also found that *p*-HCA in EPR orally administered was rapidly absorbed with a C_{max} of 10.0 min and its half-life was very short with a 30.0 ± 4.1 min, suggesting at least *p*-HCA in EPR could not affect the metabolizing enzymes of DTX (unpublished data).

However, in order to predict the adverse effects of undesirable herb-drug interactions, further studies in the liver to analyze the effects of ERP composing constituents on DTX metabolizing enzymes are required. In the present study, the pharmacokinetic profile of DTX was not significantly affected by the single EPR pretreatment. This finding may be related to the poor bioavailability of EPR being estimated from its rapid metabolism in experimental animals. Although the metabolism and pharmacokinetic characteristics of orally administered EPR as a whole extract have not yet been investigated, a few studies have described the metabolism of *p*-HCA. They have shown that *p*-HCA and its derivatives have poor bioavailability because of rapid systemic degradation in the intestinal walls and colon [20, 21].

Repeated oral administration of EPR resulted in slight increases of C_{max} and AUC_{0-t} for DTX, though the data did not reach the threshold of statistical significance (1.46-fold [p = 0.08] and 1.2-fold [p = 0.05], respectively). These results may be attributable to the accumulative effects of EPR. Although *p*-HCA has a short half-life, it cannot be ruled out that the metabolism of DTX in the liver can be modulated through continuous inhibition of CYP enzymes by the other components of EPR. The effects of repeated exposure to herbal extracts or phytochemicals originated from medicinal herbs on the metabolism of co-administered DTX were also reported by other research groups. For example, Yan *et al.* (2010) demonstrated that oral pretreatment with curcumin, a yellowish phenolic compound derived from *Curcuma longa*, for 4 consecutive days enhanced the oral bioavailability of DTX by increasing its C_{max} and AUC_{0-t} by 10- and 8-fold, respectively [22-24].

Collectively, the present study demonstrated that the pharmacokinetic profile of i.v. DTX was not significantly affected by oral EPR pretreatment, and this finding indicates the oral EPR pretreatment did not significantly modulate the pharmacokinetics of i.v. DTX at least in our animal study. However, the data suggest that the pharmacokinetics of DTX can be modulated by chronic oral EPR exposure. The underlying mechanisms of the herb-drug interactions between EPR and DTX were not clarified in this study, and therefore, further rigorous mechanism study is necessary to help predict the possible effects of these interactions and provide valuable information for the use of EPR as a supplement to support anticancer chemotherapy.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate the herb-drug interaction between EPR and DTX in terms of pharmacokinetics. Conclusively, our results demonstrate that the EPR can be used safely for combination treatment with DTX at the dose level used in this study. However, further studies in the stringent conditions for combination treatment such as administration doses, periods, and routs are required when the EPR is to be chronically consumed in combination with chemotherapeutics, especially DTX.

LIST OF ABBREVIATIONS

ANOVA	=	Analysis of variance
AUC_{0-t}	=	Area under the plasma concentration versus time curve
C_{max}	=	Maximal plasma concentration
CYP	=	Cytochrome-P450
DTX	=	Docetaxel
EPR	=	Aqueous extract of *Phragmitis rhizoma*
HCA	=	Hydroxycinnamic acid
i.v.	=	Intravenous
MRM	=	Multiple reaction monitoring
λ_Z	=	Terminal elimination rate constant
$t_{1/2}$	=	Half-life
t_R	=	Time of retention
t_{max}	=	Time to reach maximal plasma concentration
UPLC-MS/MS	=	Ultra-performance liquid chromatography- tandem mass spectrometry

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures for the animal study were reviewed and approved by the Institutional Animal Care and Use Committee of the KIOM (protocol number #17-087).

HUMAN AND ANIMAL RIGHTS

No humans were used for studies that are the basis of this research. Research work on animals was carried out in accordance with IACUC of the KIOM which follows the NC3Rs ARRIVE guidelines.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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