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Enhanced Bioavailability of Paclitaxel by Bamboo Concentrate Administration

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The purpose of this study was to investigate the effect of a cotreatment of bamboo concentrates (Jukcho solution; 0.75, 1.5, and 3.0 mL/kg) with the chemotherapeutic agent paclitaxel on the bioavailability of orally administered paclitaxel (50 mg/kg) in rats. The effect of a pretreatment of bamboo concentrates (1.5 and 3.0 mL/kg for 1.0 h or a consecutive 3 day) was also examined. The paclitaxel plasma concentrations of rats orally administered paclitaxel plus bamboo concentrates (coadministration, 3.0 mL/kg and pretreatment, 1.5 and 3.0 mL/kg) were significantly higher than those of rats treated with paclitaxel alone. Plasma concentrations of paclitaxel in groups pretreated with bamboo concentrates for 3 day were markedly higher than those of a paclitaxel control group at the measured time points. The areas under plasma concentration-time curves (AUCs) of paclitaxel in groups pretreated with bamboo concentrates were elevated and the absolute bioavailability (AB%) and relative bioavailability (RB%) of paclitaxel were also significantly higher than those in the control group. The peak concentration (C_{max}), half-life ($t_{1/2}$), and the elimination rate constant (K_{el}) of paclitaxel after 3 day of pretreatment with bamboo concentrates were also significantly higher than those in the control, but the time required to reach the maximum plasma concentration (T_{max}) of paclitaxel was unaffected by the bamboo concentrates. Western blot analyses demonstrated that the level of CYP3A4 was increased in the livers of rats treated orally with paclitaxel, but this was reversed by pretreating with bamboo concentrates. These results show that bamboo concentrates enhance the bioavailability of orally administered paclitaxel and this effect may be associated with a diminished expression of CYP3A4 in the liver.

Key words: Bamboo concentrates, Paclitaxel, Pharmacokinetic, Bioavailability, CYP3A4

INTRODUCTION

Bamboo, a large perennial grass with a woody stalk, is a common plant in Asia and its physical properties have made it useful as a natural source of pulp. It is known to have potential therapeutic activities such as antioxidative and immunomodulatory effects (Gidoh *et al.*, 1980; Shin *et al.*, 2004, Hu *et al.*, 2000; Kweon *et al.*, 2001). It has also been suggested that bamboo contains phytochemicals with cancer chemotherapeutic effects. The methanol extract of bamboo leaves induces the rapid apoptosis of human leukemia CMK-7 cells (Kim *et al.*, 2003), and a long-term treatment with the extracts of bamboo grass leaves results in a significant inhibition of both the development and growth of spontaneous mammary tumors (Tsunoda *et al.*, 1989). The anti-carcinogenesis activities of bamboo leaf extracts have also been observed using a mouse tumor model induced by benzopyrene (Kuboyama *et al.*, 1981). However, it is still unclear how bamboo extracts reduce the incidence of tumor formation in experimental models. In addition, the pharmacological effects of a combination therapy with bamboo extracts and chemotherapeutic agents have not been studied.

Paclitaxel (Taxol®) is an antineoplastic agent derived from the bark of the Pacific yew tree (*Taxus brevifolia)* (Wani *et al.*, 1971). In contrast to vinca alkaloids, the anticancer action of paclitaxel is associated with the inhibition of cellular growth by both promoting and stabilizing the microtubule assemblies as a result of its non-covalent interaction with tubulin, thereby blocking cell replication in the late G_2 mitotic phase of the cell cycle (Kumar, 1981; Manfedi and Horwitz, 1984). Paclitaxel has been used to treat many cancers for example ovarian carcinoma, breast carcinoma, leukemia, melanoma, and prostate carcinoma, and it has become particularly important for managing ovarian and breast cancer (McGuire *et al.*, 1989; Rowinsky

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et al., 1990; Holmes *et al.*, 1991; Sarosy *et al.*, 1992). However, orally administered paclitaxel is poorly absorbed due to its low solubility and multidrug efflux transporters such as P-glycoprotein (P-gp), which is abundant in the gastrointestinal tract. In addition, paclitaxel is metabolized by cytochrome P450 enzymes, particularly CYP3A and CYP2C, and it undergoes biliary excretion (Cresteil *et al.*, 1994; Kumar *et al.*, 1994; Rahman *et al.*, 1994; Sonnichsen *et al.*, 1995). Hence, paclitaxel is mainly administered intravenously (Sparreboom *et al.*, 1997). Because of its poor water solubility, paclitaxel is currently formulated as a mixture with polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol (1:1, v/v). Cremophor EL can be toxic when administered intravenously and may cause vasodilation, labored breathing, lethargy, and hypotension. In order to develop safer formulations, many studies have focused on developing new oral paclitaxel formulations. Several reports have shown that the poor bioavailability of paclitaxel may be the result of its metabolism by cytochrome P450 and counter-transport processes by P-gp. CYP3A4 and P-gp may play synergetic roles in presystemic drug metabolism (Gan *et al.*, 1996; Watkins *et al.*, 1996).

Bamboo concentrates (Jukcho solution) are concentrated solutions of the combustion products of bamboo stems according to traditional Japanese and Korean recipes. The purpose of the present study was to examine whether a co- or pre-treatment of bamboo concentrates with paclitaxel enhances the oral bioavailability of paclitaxel in rats. We found that bamboo concentrates significantly increased the bioavailability of orally administered paclitaxel, and this effect may be associated with the inhibitory effect of bamboo concentrates on the increased expression of CYP3A4 induced by paclitaxel.

MATERIALS AND METHODS

Materials

Paclitaxel was purchased from Brystol-Myers Squibb Co. (NY, USA), and saline (0.9% NaCl injectable solution) from Choongwae Co. (Seoul, Korea). Bamboo concentrates were obtained from Bamboo Tech (Damyang, Korea). Acetonitrile, methanol, and *tert*-butylmethylether were acquired from Merck Co. (Darmstadt, Germany); *n*-Butyl *p*-hydroxybenzoate (butylparaben) from Sigma (St. Louis, MO, USA); phosphoric acid from Junsei Co. (Tokyo, Japan); and anti-CYP3A4 IgG from Detroit R&D (Detroit, MI, USA). Other chemicals were of reagent grade and used without further purification. The apparatus used included a high performance liquid chromatograph (HPLC, a Waters 1515 isocratic HPLC Pump, a Waters 717 plus autosampler, a Waters 2487 Dual I absorbance detector, Waters Co., Milford, MA, USA), a centrifugal evaporator (Rikakikai Co., Japan), a mechanical stirrer (Scientific Industries, USA), a centrifuge (Hanil Science Industrial Co., Korea), a microcentrifuge (National Labnet, USA), a sonicator (Daihan Co., Korea), a refrigerated bath circulator and a rotamix (Seolin Biosience, Korea).

Animal experiments and drug administration

Male Sprague-Dawley rats (270-300 g) were purchased from Dae-Han Laboratory Animal Research (Eumsung, Korea), and they had free access to normal standard chow diet (Jae Il Chow, Korea) and tap water prior to the experiments. Throughout the experiments, animals were maintained under 12 h light and dark cycles in an air-conditioned room (22 ± 2°C, 50-60% relative humidity) with commercially-available rat chow (Purina, Korea) and water available *ad libitum*. The animals were kept in these facilities for at least 1 week before the experiments. Experiments were carried out in accordance with the "Guiding Principles for the use of Animals in Toxicology" adopted by the Society of Toxicology (USA) in July 1989 and revised in March 1999. The animal care committee at our institution (Chosun University) approved the present study.

The rats were fasted for 24 h prior to the experiments. Animals were anaesthetized with ethyl ether. The right femoral artery was cannulated with polyethylene tubing (PE-50, Intramedic, Clay Adams, NJ, USA) for blood sampling. A dose of paclitaxel (50 mg/kg) was chosen to maintain plasma concentrations above the limit of detection at 24 h after treatment. Paclitaxel was prepared in suspension by adding paclitaxel (50 mg/kg) to distilled water (1.2 mL) containing Tween80 (10 μL) and stirred for 1 h for the control group. The paclitaxel and bamboo concentrate mixtures for the coadministration group were prepared from 1.0 mL of paclitaxel (50 mg/kg) suspension with bamboo concentrates (0.75, 1.5 or 3.0 mL/kg). For the pretreated group, bamboo concentrates (1.5 and 3.0 mL/kg) were administered 1 h before the paclitaxel treatment or for 3 consecutive days (twice per day) prior to the administration of paclitaxel. It was assumed that the administration of paclitaxel for 3 days would cause a change in the expression levels of drug metabolizing enzymes. Blood samples (0.6 mL) were collected from the femoral artery at 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h after the administration. In order to evaluate the absolute bioavailability of paclitaxel, 0.5 mL of injectable paclitaxel solution (2 mg/kg) was injected through the femoral vein slowly. Blood samples were centrifuged at 5,000 rpm for 5 min, and plasmas were stored at -40°C until required for HPLC analysis. Data were obtained from at least four independent experiments. After blood sampling, livers were collected and stored at -70°C until examined to determine CYP3A4 levels.

HPLC assay

Plasma paclitaxel concentrations were determined by HPLC using a modification of the method reported by Lee *et al.*, (1999) and Mase *et al.* (1994). Briefly, 50 μL of *n*-butyl *p*-hydroxybenzoate (2 μg/mL), as an internal standard, and 4 mL of *tert*-butylmethylether were added to 0.25 mL of a plasma sample and mixed for 20 min using a rotamix then centrifuged at 5,000 rpm for 15 min. Three milliliters of the organic layer was then transferred to a clean test tube and evaporated in a centrifugal evaporator at 30°C. The residue was then dissolved in a 0.5 g/mL zinc sulfate solution [zinc sulfate : methanol : ethylene glycol (0.5 g:100 mL:1 mL)] and centrifuged at 5,000 rpm for 5min; 50 μL of this solution was injected into the HPLC system.

The HPLC system consisted of a Waters 1515 isocratic HPLC Pump, a Waters 717 plus autosampler, a Waters 2487 Dual I absorbance detector (Waters Co., Milford, MA, USA) and an integrator. The detector wavelength was set at 227 nm and the column was used at room temperature. The column was a Symmetry C_{18} column (4.6×150 mm, 5 μm, Waters Co., USA). A mixture of acetonitrile: methanol: 0.05 mM phosphate buffer (pH 4.0) (45: 10: 45 v/v/v) was used as the mobile phase at a flow rate of 1.2 mL/min. The retention times of the internal standard and paclitaxel were 5.3 and 7.7 min, respectively.

Pharmacokinetic analysis

One compartment open model pharmacokinetics paramenters were calculated by nonlinear least square regression using MULTI (Yamaoka *et al.*, 1981). The parameters were fitted using the simplex method when Akaike's information criterion (the AIC value) was lowest. Areas under the plasma concentration-time curve (AUCs) were calculated using the trapezoidal rule.

The maximum plasma concentration (C_{max}) and the time required to reach the maximum plasma concentration (T_{max}) were determined by visual inspection of the experimental data. The elimination rate constant (K_{el}) was calculated by regression analysis from the slope of the line, and the half-life ($t_{1/2}$) was obtained using $0.693/K_{el}$. The absolute bioavailability of paclitaxel after an oral administration (50 mg/kg) versus IV administration (2 mg/kg) was calculated as follows:

$$\text{Absolute bioavailability (AB\%)} = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{\text{IV dose}}{\text{Oral dose}} \times 100$$

The relative bioavailability of paclitaxel after an oral administration was calculated as follows:

$$\text{Relative bioavailability (RB\%)} = \frac{AUC_{coadmin}}{AUC_{control}} \times 100$$

Isolation of microsomal proteins

Hepatic microsomal fractions prepared by differential centrifugation were washed in pyrophosphate buffer and stored in 50 mM Tris-acetate buffer (pH 7.4) containing 1 mM EDTA and 20% glycerol. Samples were stored at -70 °C until required. The protein content was determined using a protein assay kit (Bio-Rad Laboratories, Hercules, CA).

Immunoblot analysis

Sodium dodecylsulfate-polyacrylamide gel electrophoresis was carried out according to previously published procedures (Kim and Cho, 1996). Microsomal proteins were separated in 7.5% gels and electrophoretically transferred to nitrocellulose paper, which was then incubated with anti-rat cytochrome P450 antibody and incubated with HRP-conjugated secondary antibody. For P450 immunoblottings, filters were allowed to react with mouse monoclonal anti-P450 3A4 (3A23) antibody (Detroit R&D, MI) or mouse monoclonal anti-actin antibody (1:20,000, Sigma, MO) and then further incubated with alkaline phosphatase or horseradish peroxidase-conjugated goat anti-mouse IgG as a secondary antibody. Blots were finally developed using 5-bromo-4-chloro-3-indoylphosphate and nitroblue tetrazolium or an ECL chemiluminescence detection kit.

Statistical analysis

All means are presented with their standard deviations (Mean±SD). The paired Student's *t-test* was used to determine a significance difference between the paclitaxel control and the paclitaxel cotreated or pretreated with bamboo concentrates group. Differences were considered to be significant at $p < 0.05$.

RESULTS AND DISCUSSION

The plasma concentrations of paclitaxel (administered at 50 mg/kg) after an oral coadministration (0.75, 1.5 or 3.0 mL/kg) and pretreatment (1.5 or 3.0 mL/kg, pretreated for 1 h or 3 consecutive day) of bamboo concentrates are shown in Figs. 1 and 2 respectively. The pharmacokinetic parameters of paclitaxel after the oral coadministration and pretreatment with bamboo concentrates are shown in Tables I and II respectively.

The plasma concentration of paclitaxel after the oral coadministration with the bamboo concentrates at 3.0 mL/kg was significantly increased at 12 and 24 h compared to that of the paclitaxel control group (Fig. 1). The coadministration of low doses of bamboo concentrates (0.75 and 1.5 mL/kg) did not affect the plasma concentration of paclitaxel (Fig. 1). After coadministering 3 mL/kg of bamboo concentrates, the AUC of paclitaxel was significantly

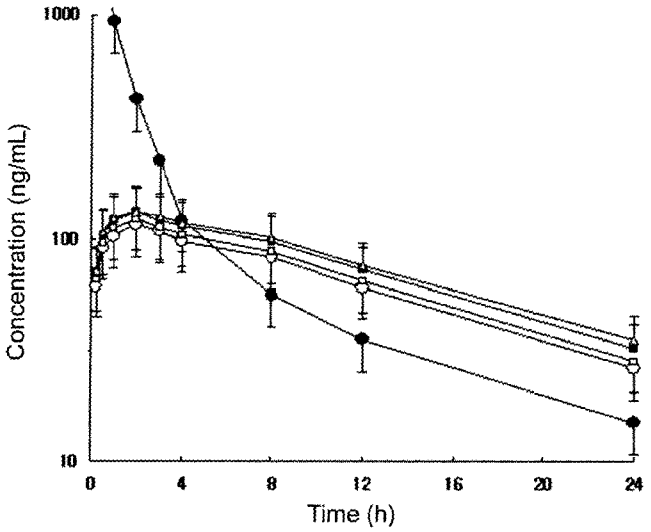

Fig. 1. Mean plasma concentration-time profiles of paclitaxel (50 mg/kg) coadministered with bamboo concentrates in rats. Bars represent the standard deviation. (n=6). (○) Control (paclitaxel 50 mg/kg); (●) iv (paclitaxel 2.0 mg/kg); (□) coadministered with bamboo concentrates 0.75 mL/kg; (■) coadministered with bamboo concentrates 1.5 mL/kg; (△) coadministered with bamboo concentrates 3 mL/kg.

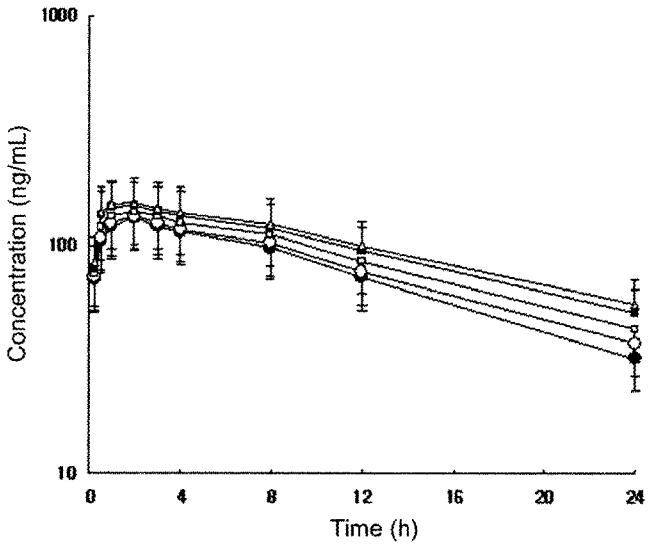

Fig. 2. Mean plasma concentration-time profiles of paclitaxel after a pretreatment with bamboo concentrates in rats. Bars represent the standard deviation (n=6). (●) Control (paclitaxel 50 mg/kg); (○) pretreated with bamboo concentrates 1.5 mL/kg 1 h before; (□) pretreated with bamboo concentrates 3.0 mL/kg 1 h before; (■) pretreated with bamboo concentrates 1.5 mL/kg 3 day before; (△) pretreated with bamboo concentrates 3.0 mL/kg 3 day before.

higher (1837±459 vs 2370±639, $p<0.05$) than that of the control group, and the absolute bioavailability (AB) of paclitaxel was also significantly increased from 2.0 (Control) to 2.6, while the relative bioavailability (RB) of paclitaxel was not affected by the coadministration of bamboo concentrates (Table I).

The plasma concentrations of paclitaxel in rats pretreated with bamboo concentrates (1.5 and 3.0 mL/kg for 3 day) were higher than those of the control group at the measured time points (8-24 h) (Fig. 2). The AUCs of paclitaxel of rats pretreated with bamboo concentrates (3.0 mL/kg for 3 day) were increased up to 46%, and the AB of paclitaxel was also significantly higher (from 2.0 to 3.7) than that of the control group. The RB of paclitaxel was also enhanced by 181% (Table II). The C_{max}, K_{el}, and half-life ($t_{1/2}$) of paclitaxel after 3 days of pretreatment with bamboo concentrates were significantly higher than those of the control, but the T_{max} of paclitaxel was not affected by the bamboo concentrates (Table II).

Table I. Mean pharmacokinetic parameters of paclitaxel (50 mg/kg) after an oral coadministration with bamboo concentrates in rats

Parameters	Paclitaxel	Bamboo coadmin.			
	IV (2 mg/kg)	Control	0.75 mL/kg	1.5 mL/kg	3.0 mL/kg
AUC (ng/mL·h)	3631±907	1837±459	2030±508	2223±569	2370±639*
C_{max}(ng/mL)		115±29	122±31	132±34	135±34
T_{max}(h)		2.0±0.6	2.0±0.5	1.9±0.5	1.8±0.5
K_{el}(h^{-1})	0.082±0.021	0.070±0.017	0.067±0.016	0.064±0.016	0.060±0.014
$t_{1/2}$ (h)	8.40±2.11	9.90±2.47	10.34±2.58	10.72±2.63	11.55±2.68
AB(%)		2.0	2.2	2.5	2.6*
RB(%)		100	110	121	129

Mean±S.D. (n = 6), *p<0.05 compared to the control
AUC: area under the plasma concentration-time curve
C_{max}: peak concentration
T_{max}: time to reach peak concentration
K_{el}: elimination rate constant
$t_{1/2}$: half-life
AB(%): absolute bioavailability
RB(%): comparative $AUC_{coad.}/AUC_{po}$

Table II. Mean pharmacokinetic parameters of oral paclitaxel (50 mg/kg) after a pretreatment with bamboo concentrates for 1.0 h or 3 day in rats

Parameters	Control	Bamboo Pretreat.			
		1.0 h (1.5 mL/kg)	1.0 h (3.0 mL/kg)	3 days (1.5 mL/kg)	3 days (3.0 mL/kg)
AUC (ng/mL·h)	1837±459	2425±588*	2639±659*	3123±824**	3326±853**
C_{max}(ng/mL)	115±29	134±34	137±34	149±38*	153±41*
T_{max}(h)	2.0±0.6	1.9±0.5	1.8±0.5	1.6±0.4	1.7±0.4
$K_{el}(h^{-1})$	0.070±0.017	0.064±0.016	0.056±0.014	0.050±0.013*	0.049±0.012*
$t_{1/2}$ (h)	9.90±2.47	10.72±2.63	12.38±2.98	13.86±3.34*	14.14±3.48*
AB(%)	2.0	2.7*	2.9*	3.5**	3.7**
RB(%)	100	132	144	170	181

Mean±S.D. ($n = 6$), *$p<0.05$, **$p<0.01$ compared to the control
AUC: area under the plasma concentration-time curve
C_{max}: peak concentration
T_{max}: time to reach peak concentration
K_{el}: elimination rate constant
$t_{1/2}$: half-life
AB(%): absolute bioavailability
RB(%): comparative $AUC_{pretreat.}/AUC_{po}$

Orally administered paclitaxel is poorly absorbed due to its low solubility and the efflux pump function of the multi-drug efflux transporter P-gp in the gastrointestinal tract. Paclitaxel is also metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4, and it undergoes biliary excretion (Cresteil *et al.*, 1994; Kumar *et al.*, 1994; Rahman *et al.*, 1994; Sonnichsen *et al.*, 1995). The poor bioavailability of oral paclitaxel may be the result of its low absorption and intensive metabolism by cytochrome P450 enzymes. In the present study, the AUC, C_{max} and AB of paclitaxel after the oral coadministration or pretreatment of bamboo concentrates were higher than those of the control, and these were more significant for the pretreated groups. These effects may be due to the inhibition of the paclitaxel efflux in the intestinal mucosa or metabolism in the liver by bamboo concentrates. The bamboo extracts significantly increased the plasma concentration of orally treated paclitaxel, especially at later time points, suggesting that the first-pass metabolism of paclitaxel by CYP3A4 may be reduced by a pretreatment with bamboo concentrates.

The levels of CYP3A4 in the livers of rats treated with paclitaxel and bamboo concentrates were monitored in order to determine if the concentrates affected its expression level. Paclitaxel at 50 mg/kg slightly increased the CYP3A4 protein level in the liver, which is consistent with the observation that docetaxel increases the expression of CYP3A4, but not that of CYP2C (Fujitaka *et al.*, 2001). Studies were extended to assess whether the extent of the CYP3A4 expression was affected by the 3 day of consecutive treatment with bamboo concentrates (Fig. 3). In rats pretreated with bamboo concentrates (1.5 and 3.0 mL/kg), the paclitaxel-inducible CYP34A expression was decreased (Fig. 3). These results confirm the possibility

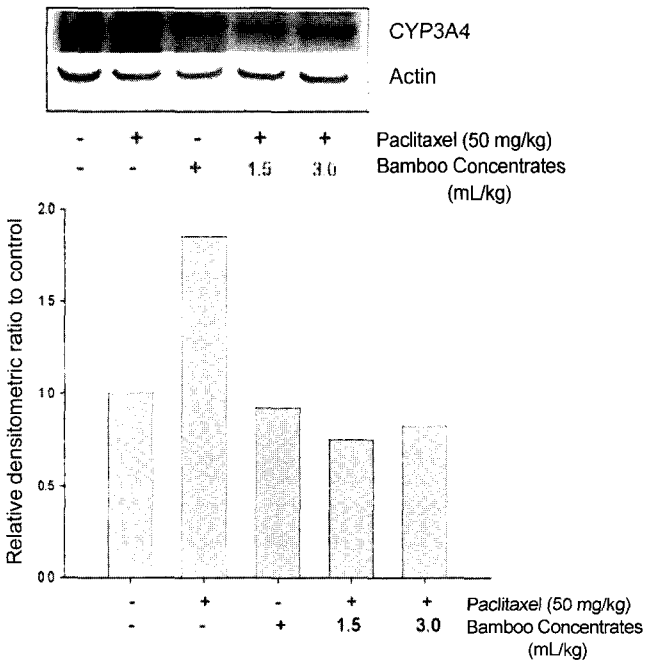

Fig. 3. Hepatic CYP3A4 expression after a treatment with paclitaxel and bamboo concentrates. An immunoblot analysis of CYP3A4 was carried out on rat hepatic microsomal proteins isolated from rats orally treated with vehicle, paclitaxel (50 mg/kg), or paclitaxel plus bamboo concentrates (1.5 mL/kg and 3.0 mL/kg for 3 day). Each lane was loaded with 10 μg of protein. Membranes were re-incubated with an actin antibody as a loading control. Relative changes in the level of CYP3A4 were assessed by scanning densitometry. Results were confirmed by at least 3 repeated experiments.

that the increased plasma concentration of paclitaxel in rats pretreated with bamboo concentrates might be asso ciated with the diminished CYP3A4 expression in the liver.

In conclusion, the current study demonstrates that bamboo concentrates increase the bioavailability of orally treated paclitaxel in rats. Since CYP3A4 is involved in the metabolism of paclitaxel and affects its pharmacokinetic profile, the reduced expression of CYP3A4 by bamboo concentrates may increase the bioavailability of paclitaxel. In addition, it would be helpful as a new pharmaceutical composition of paclitaxel if an oral preparation of paclitaxel and bamboo concentrates was developed.

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