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Enhanced paclitaxel bioavailability after oral coadministration of paclitaxel prodrug with naringin to rats

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Abstract

The aim of this study was to investigate the effect of naringin on the bioavailability and pharmacokinetics of paclitaxel after oral administration of paclitaxel or its prodrug coadministered with naringin to rats. Paclitaxel (40 mg/kg) and prodrug (280, 40 mg/kg paclitaxel equivalent) were coadministered orally to rats with naringin (1, 3, 10 and 20 mg/kg).

The plasma concentrations of paclitaxel coadministered with naringin increased significantly ($p < 0.01$ at paclitaxel, $p < 0.05$ at prodrug) compared to the control. The areas under the plasma concentration–time curve (AUC) and the peak concentrations (C_{max}) of paclitaxel with naringin significantly higher ($p < 0.01$) than the control. The half-life ($t_{1/2}$) was significantly ($p < 0.05$) longer than the control. The absolute bioavailability (AB, %) of paclitaxel with naringin was significantly higher (3.5–6.8%, $p < 0.01$) than the control (2.2%). Absorption rate constant (K_a) of paclitaxel with naringin increased, but not significantly. The AUC of paclitaxel after coadministration of prodrug with naringin to rats was significantly ($p < 0.05$) higher than the prodrug control. The relative bioavailability (RB, %) of paclitaxel after coadministration of prodrug with naringin was 1.35–1.69-fold higher than prodrug control. The absolute bioavailability (AB, %) of paclitaxel after coadministration of prodrug with naringin increased significantly ($p < 0.05$) from 6.6 to 9.0% and 11.2%. The bioavailability of paclitaxel coadministered as a prodrug with or without naringin was remarkably higher than the control. Paclitaxel prodrug, a water-soluble compound concerning with its physicochemical properties, passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa. Oral paclitaxel preparations which is more convenient than the IV dosage forms could be developed with a prodrug form with naringin.

Keywords: Paclitaxel; Prodrug; Naringin; Pharmacokinetic; Bioavailability; Coadministration

1. Introduction

Paclitaxel (Taxol®) is an antineoplastic agent that is derived from the bark of the Pacific yew tree (*Taxus*

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brevifolia) (Wani et al., 1971). In contrast to Vinca alkaloids, the anticancer action of taxol is that it inhibits cellular growth by promoting and stabilizing the microtubule assembly by a non-covalent interaction with tubulin, which blocks cell replication in the late G_2 mitotic phase of the cell cycle (Kumar, 1981; Manfedi and Horwitz, 1984). Because of its poor water solubility, paclitaxel is currently dissolved in a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol (1:1, v/v) for the IV dosage form. However, Cremophor EL itself is toxic and produces vasodilation, labored breathing, lethargy and hypotension when administered intravenously. One mediator of the hypersensitivity reactions is the endogenous histamine release and prophylaxis to counteract the histaminergic mechanisms and reduces the incidence of the hypersensitivity reactions (Rowinsly et al., 1993).

Paclitaxel has been used to treat ovarian carcinoma, breast carcinoma, leukemia, melanoma, prostate carcinoma, etc., and has become particularly important in managing ovarian and breast carcinoma (Rowinsky et al., 1990; McGuire et al., 1989; Sarosy et al., 1992; Holmes et al., 1991). The oral administration of the paclitaxel is problematic as it has poor absorption due to the poor solubility and efflux pump function of the drug for the multidrug transporter P-glycoprotein (P-gp), which is present abundantly in the gastrointestinal tract. Thus, this drug is mainly used for intravenous administration (Sparreboom et al., 1997).

Paclitaxel has a very large volume of distribution in the body, and is highly bound by the plasma protein, primarily albumin (95–98%) (Wiernik et al., 1987). In particular, it is much higher in the disposition of the liver and bile than in the other tissues (Fujita et al., 1994). Less than 6–10% of administered paclitaxel is recovered as the unchanged drug in the urine of treated patients (Wiernik et al., 1987; Brown et al., 1997). Paclitaxel is mainly metabolized though the liver and undergoes biliary excretion (Cresteil et al., 1994; Kumar et al., 1994; Rahman et al., 1994; Sonnichsen et al., 1995). In humans, the total fecal excretion is approximately 70% of the paclitaxel dose, with 6α-hydroxypaclitaxel being the major metabolite (Walle et al., 1995).

In an attempt to develop safer formulations, many studies have been directed towards a new oral formulation. However, paclitaxel is very poorly absorbed when administered orally. Several studies have reported that the poor bioavailability of paclitaxel would result from the metabolism by enzymes or counter-transport processes by P-gp in the gut wall. It has been suggested that, in some cases the poor absorption of drugs after oral administration results from the activity of a multidrug transporter, a membrane-bound P-gp, which functions as an energy-dependent transporter or an efflux pump to decrease the intracellular accumulation of the drugs by extruding xenobiotics from the cell (Sparreboom et al., 1997).

Flavonoids are regarded as a new class of chemosensitizers, which interact with both the cytosolic domains of P-gp and its ATP binding site (Conseil et al., 1998) and various CYP enzyme inhibitors (Peter et al., 2002). It also has been reported to have antiproliferative effect on cancer cell (Darwanto et al., 2000) and peroxidation activity and antioxidant agents (Ferguson, 2001), which exist in various plants and vegetable food as glycosides (Scambia et al., 1995).

Naringin as a member of the flavonoids class has been reported to possess the ability to inhibition of the P-gp efflux pump (Conseil et al., 1998; Scambia et al., 1995; Bailey et al., 1993; Takanaga et al., 1998). It also has been reported that naringin can inhibit CYP 3A, which is the main subfamily of the cytochrome P450 that is responsible for metabolizing paclitaxel (Kumar et al., 1994; Peter et al., 2002; Doostdar et al., 2000; Dupuy et al., 2003; Hodek et al., 2002). Quercetin, flavone, naringin, GF120918 and cyclosporine as the inhibitors of CYP3A and P-pg, have increased the bioavailability of some drugs, which are substrates of CYP3A and P-pg (Scambia et al., 1995; Bailey et al., 1993; Takanaga et al., 1998; Zhang et al., 2000; Choi et al., 2004a, 2004b; Bardelmeijer et al., 2000; Malingre et al., 2001). But there is no investigation about naringin if it potentiates the ability of inhibition of P-gp and CYP enzymes or not, with paclitaxel administered orally to rats.

A water-soluble prodrug compound, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, was synthesized with a water-soluble polymer and paclitaxel (Jo, 2004). It is rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel.

The purpose of this study was to investigate the bioavailability of paclitaxel after oral administration of paclitaxel and paclitaxel prodrug alone or with naringin.

2. Materials and methods

2.1. Materials

Paclitaxel was purchased from Brystol-Myers Squibb Co. (NY, USA). Saline (0.9% NaCl injectable solution) was obtained from Choongwae Co. (Seoul, Korea). Acetonitrile, methanol, *tert*-butylmethylether were acquired from Merck Co. (Darmstadt, Germany). Naringin and *n*-butyl *p*-hydroxybenzoate (butylparaben) was purchased from the Sigma Chemical Co. (St. Louis, MO, USA). Phosphoric acid was obtained from the Junsei Co. (Tokyo, Japan). The other chemicals were of reagent grade and were used without further purification. The apparatus were used high performance liquid chromatography (HPLC, Waters 1515 isocratic HPLC Pump, Waters 717 plus autosampler, Waters 2487 Dual λ absorbance detector, Waters Co., Milford, MA, USA).

2.2. Synthesis of prodrug

A water-soluble prodrug compound was obtained by introducing a new self-immolating linker that spontaneously decomposes into paclitaxel and a water-soluble polymer, and combines the water-soluble polymer with the resulting product. The prodrug compound is rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel (Jo, 2004). The prodrug, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, was synthesized as follows.

7-Chloromethyloxycarbonyl-paclitaxel (1.057 mmol) was dissolved in anhydrous benzene. Monomethoxypolyethyleneglycol 5000-succinate (1.057 mmol), sodium iodide (3.171 mmol), potassium carbonate (1.902 mmol) and 18-crown-6 ether (0.739 mmol) were mixed in the resulting solution. The mixture was stirred for 36 h under reflux and dried under reduced pressure to remove the benzene, and then dissolved in dichloromethane. The obtained material was filtered to remove the un-dissolved material. The organic layer was washed twice with water, and the separated organic layer was dehydrated over anhydrous magnesium sulfate, dried under reduced pressure and recrystallized from isopropyl alcohol to obtain the solid material. The solid material was purified with HPLC for collection (Prep-HPLC) by yield of 68%. NMR showed the peaks like following; (300 MHz, $CDCl_3$) δ 4.39–3.38 (m, mPEG), 5.88 (d, 1H, $J = 5.85$ Hz, $OCOOCH_2O$), 5.71 (d, 1H, $J = 5.85$ Hz, $OCOOCH_2O$). A more detailed procedure will be appeared elsewhere (Sohn et al., 2003; Jo, 2000).

2.3. Animal experiments and drug administration

Male Sprague-Dawley rats (270–300 g) were purchased from Daehan Laboratory Animal Research and Co. (Choongbuk, Korea), and had free access to normal standard chow diet (JaeIl Chow, Korea) and tap water. Throughout the experiment, the animals were housed, four or five per cage, in laminar flow cages maintained at $22 \pm 2\,^{\circ}C$, 50–60% relative humidity, under a 12 h light-dark cycle. The animals were kept in these facilities for at least 1 week before the experiment. This experiment was carried out in accordance with the "Guiding Principles in 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 in our institution (Chosun University) approved the present study.

Sprague-Dawley rats were fasted for at least 24 h prior to experiments and were given water freely. Each rat was anaesthetized with ether. The right femoral artery was cannulated with polyethylene tubing for blood sampling. Paclitaxel suspension was prepared by adding paclitaxel (40 mg/kg) to distilled water (1.2 ml) containing Tween 80 (10 μl) and stirring for 1 h. Paclitaxel dose (40 mg/kg) was chosen to keep plasma concentration above the limit of detection at 24 h. Paclitaxel suspension was prepared by adding paclitaxel (40 mg/kg) and naringin (1, 3, 10, 20 mg/kg) to distilled water (1.2 ml) containing Tween 80 (10 μl) and stirring for 1 h. Paclitaxel prodrug solution was prepared by adding paclitaxel prodrug (280 mg/kg) and naringin (1, 3, 10 mg/kg) to distilled water (1.2 ml) containing Tween 80 (10 μl) and stirring for 1 h. The paclitaxel suspension or the prodrug solution was administered to rats orally. Blood samples (0.6 ml) were withdrawn from the femoral artery at 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h after the oral administration of the drug. The plasma samples were centrifuged at 5000 rpm for 5 min. The plasmas were stored at $-40\,^{\circ}C$ until the HPLC analysis.

2.4. HPLC assay

The plasma concentrations of paclitaxel were determined by the modified HPLC method reported by Lee and Mase (Lee et al., 1994; Yamaoka et al., 1981). Briefly, 50 μl of *n*-butyl *p*-hydroxybenzoate (2 μg/ml), as the internal standard, and 4 ml of *tert*-butylmethylether were added to 0.25 ml of the plasma samples. It was then mixed for 20 min using the rotamix and centrifuged at 5000 rpm for 15 min. Three milliliters of the organic layer were 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 5000 rpm for 5 min, and a 50 μl of the solution was injected into the HPLC system. The HPLC system consisted of a Waters 1515 isocratic HPLC Pump, a Waters 717 plus auto sampler, a Waters 2487 Dual λ absorbance detector (Waters Co., Milford, MA, USA) and a computing integrator. The detector wavelength was set at 227 nm and the column was used at room temperature. The column used was a Symmetry C_{18} column (4.6 mm × 150 mm, 5 μm, Waters Co., USA). Mixtures of acetonitrile:methanol:0.05 mM phosphate buffer (pH 4.0) (45:10:45, v/v/v) were used as the mobile phases at a flow rate of 1.2 ml/min. The retention times were as follows: internal standard, 5.3 min and paclitaxel, 7.7 min.

2.5. Pharmacokinetic analysis

Pharmacokinetic parameters in terms one compartment open model were calculated with a nonlinear least square regression using a MULTI program (40). The parameter value was obtained fitted to simplex method when AIC (Akaike's information criterion) value was the lowest. The area under the plasma concentration–time curves (AUC) was calculated by trapezoidal rule. The maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) were determined by a 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 ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$.

The absolute bioavailability of paclitaxel after the oral administration (40 mg/kg) compared to the IV administration (2 mg/kg) was calculated as follows:

$$\text{absolute bioavailabillity (AB)} = \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{IV}}} \times \frac{\text{IV dose}}{\text{oral dose}} \times 100$$

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

$$\text{relative bioavailability} = \frac{\text{AUC}_{\text{coadmin.}}}{\text{AUC}_{\text{control}}} \times 100$$

2.6. Statistical analysis

All the means are presented with their standard deviation (mean ± S.D.). An unpaired Student's *t*-test was used to determine any significance difference between the controls and prodrug pretreated with naringin. The differences were considered to be significant at $p < 0.05$.

3. Results and discussion

3.1. Plasma concentration of paclitaxel from the prodrug with naringin

The plasma profiles of paclitaxel after the oral administration of the paclitaxel control (40 mg/kg) and the prodrug (280, 40 mg/kg paclitaxel equivalent) coadministered with various dose of naringin (1, 3,10 and 20 mg/kg) are shown in Figs. 1 and 2. The bioavailability and the pharmacokinetic parameters of paclitaxel after the administration of paclitaxel or prodrug coadministered with naringin are shown in Tables 1 and 2. When paclitaxel (40 mg/kg) or prodrug (280 mg/kg) was coadministered with naringin, the plasma concentrations of paclitaxel were increased significantly ($p < 0.01$ at paclitaxel, $p < 0.05$ at prodrug) compared to the control.

3.2. Bioavailability and pharmacokinetic parameters of paclitaxel from the prodrug with naringin

After the oral administration of paclitaxel or prodrug with naringin, the AUC and C_{max} of paclitaxel were in-

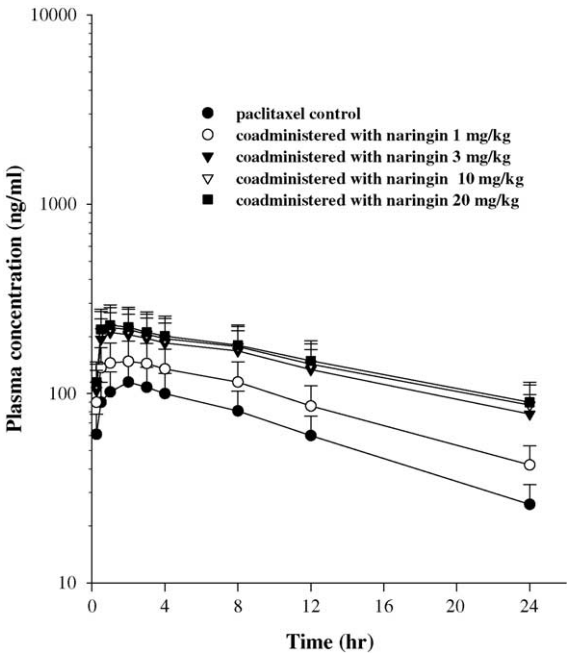

Fig. 1. Mean plasma concentration–time profiles of paclitaxel after oral coadministration of paclitaxel (40 mg/kg) with naringin to rats. Bars represent the standard deviation ($n = 6$).

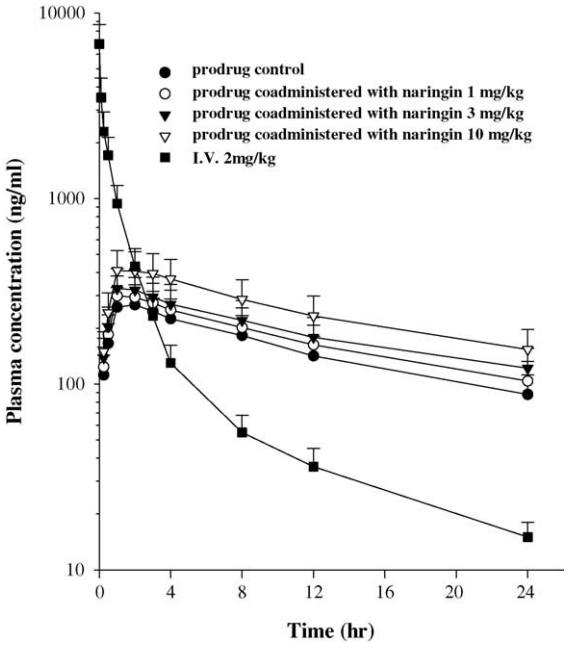

Fig. 2. Mean plasma concentration–time profiles of paclitaxel after oral coadministration of prodrug (280, 40 mg/kg paclitaxel equivalent) with naringin to rats. Bars represent the standard deviation ($n = 6$).

creased significantly ($p < 0.01$ at paclitaxel, $p < 0.05$ at prodrug) compared to the control. The $t_{1/2}$ of paclitaxel or prodrug with naringin were prolonged significantly ($p < 0.05$) compared to the control. Absorption rate constant (K_a) was increased but not significant.

The absolute bioavailability (AB, %) of the paclitaxel control was 2.2, which was increased significantly ($p < 0.01$ at paclitaxel, $p < 0.05$ at prodrug) by naringin (range between 3.5–6.8 in paclitaxel and 6.6–11.2 in prodrug). The relative bioavailability (RB, %) of paclitaxel with naringin was 1.52–3.02-fold higher.

These results were consistent with the result reported by Scambia et al. and Choi et al. (Scambia et al., 1995; Zhang et al., 2000; Choi et al., 2004a, 2004b), in that flavonoid (quercetin and flavone) increased bioavailability of paclitaxel and adriamycin and quinine by inhibition of P-gp pump efflux or cytochrome P-450 (CYP 3A). This result was also consistent with the result reported by Bardelmeijer et al. and Malingre et al. (33–34), in that GF 120918 and cyclosporine increased bioavailability of paclitaxel and docetaxel, respectively.

Paclitaxel is reported to be metabolized by cytochrome P-450 (CYP3A) in both the liver and epithelial cells of small intestine (Cresteil et al., 1994; Kumar et al., 1994; Rahman et al., 1994; Sonnichsen et al., 1995). In addition, the absorption of paclitaxel was inhibited by the P-pg efflux pump in the intestinal mucosa (Sparreboom et al., 1997; Bardelmeijer et al., 2000). Naringin affected the bioavailability of paclitaxel similar to those of quercetin, flavone and GF 120918, which are the inhibitors of CYP 3A and P-gp. It might be considered that the bioavailability of paclitaxel with naringin was P-gp pump efflux or cytochrome P-450 (CYP 3A) significantly enhanced due to both the inhibition of cytochrome P-450 and the P-gp efflux pump in the intestinal mucosa.

The study on the water-soluble prodrug compound, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, which was obtained by introducing a new self-immolating linker that is spontaneously decomposed into paclitaxel combining a water-soluble polymer (Jo, 2000, 2004; Sohn et al., 2003) was conducted. The AB (%) of paclitaxel in the prodrug control was 6.6,

Table 1
Pharmacokinetic parameters of paclitaxel after oral coadministration of paclitaxel (40 mg/kg) with naringin in rats

Parameter	Paclitaxel control	Naringin coadministration			
		1 mg/kg	3 mg/kg	10 mg/kg	20 mg/kg
K_a (h^{-1})	2.53 ± 0.64	3.06 ± 0.72	3.10 ± 0.71	3.12 ± 0.79	3.120.80
AUC_{0-22} (ng/ml h)	1931 ± 523	2961 ± 743*	5103 ± 1026**	5668 ± 1424**	5827 ± 1432**
C_{max} (ng/ml)	115 ± 29.8	148 ± 40.2	209 ± 53.3**	223 ± 54.5**	230 ± 56.3**
T_{max} (h)	1.6 ± 0.61	1.3 ± 0.31	1.3 ± 0.42	1.2 ± 0.41	1.3 ± 0.42
$t_{1/2}$ (h)	10.62 ± 2.48	12.62 ± 3.09	15.75 ± 3.88*	16.12 ± 4.28*	16.50 ± 4.32*
AB (%)	2.2	3.5*	5.9**	6.6**	6.8**
RB (%)	100	152	263	294	302

Mean ± S.D. ($n = 6$). K_a: absorption rate constant; AUC_{0-22} area under the plasma concentration–time curve from 0 to 22 h; C_{max}: peak concentration; T_{max}: time to reach peak concentration; $t_{1/2}$: terminal half-life; AB (%): absolute bioavailability; RB (%): AUC rate compared to AUC control.

* $p < 0.05$ compared to control.

** $p < 0.01$ compared to control.

and that with naringin increased significantly ($p < 0.05$ at 10 mg/kg) to 7.8 and 11.2%. The RB (%) was increased approximately 116–169% compared to the prodrug control. These results suggested that the bioavailability of paclitaxel in the prodrug was also promoted by naringin, as mentioned above due to its potency of P-gp and cytochrome P-450 inhibition in the gastrointestinal mucosa.

The molecular weight of paclitaxel and prodrug is approximately 700 and 5000, respectively, and the bioavailability of paclitaxel as a result of administration of the prodrug with or without naringin were remarkably higher than the paclitaxel control, which was more than three- and four- to five-fold with naringin. It might have resulted from the physicochemical properties of the prodrug, which is a water soluble compound and passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa and it can be rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel (Choi et al., 2004a, 2004b), and leads to a high concentration of paclitaxel in the plasma to make the higher bioavailability than the parent drug.

Based on these results, it might be feasible to develop an oral paclitaxel preparation, which is more convenient than the IV dosage forms.

Table 2
Pharmacokinetic parameters of paclitaxel after oral coadministration of paclitaxel prodrug (280, 40 mg/kg paclitaxel equivalent) with naringin to rats

Parameters	Prodrug control	Naringin coadministration			
		1 mg/kg	3 mg/kg	10 mg/kg	IV
K_a (h^{-1})	2.0 ± 0.60	2.1 ± 0.61	2.2 ± 0.63	2.1 ± 0.62	
AUC_{0-22} (ng/ml h)	5668 ± 1409	6671 ± 1653	7769 ± 1825*	9589 ± 2196**	4296 ± 1124
C_{max} (ng/ml)	268 ± 68	299 ± 74	328 ± 79	410 ± 103**	
T_{max} (h)	1.9 ± 0.56	1.8 ± 0.55	1.7 ± 0.55	1.8 ± 0.57	
$t_{1/2}$ (h)	12.6 ± 3.02	13.4 ± 3.21	14.1 ± 3.27	14.9 ± 3.18*	8.2 ± 2.3
AB (%)	6.6	7.8	9.0*	11.2**	100
RB (%)	100	116	135	169	

Mean ± S.D. ($n = 6$). K_a: absorption rate constant; AUC_{0-22} area under the plasma concentration–time curve from 0 to 22 h; C_{max}: peak concentration; T_{max}: time to reach peak concentration; $t_{1/2}$: terminal half-life; AB (%): absolute bioavailability; RB (%): AUC rate compared to AUC control.

* $p < 0.05$ compared to control.

** $p < 0.01$ compared to control.

4. Conclusion

Paclitaxel prodrug, a water-soluble compound concerning with its physicochemical properties, passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa. Oral paclitaxel preparations which is more convenient than the IV dosage forms could be developed with a prodrug form with naringin.

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