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Effect of genistein on the pharmacokinetics of paclitaxel administered orally or intravenously in rats

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Abstract

As many anticancer agents paclitaxel is a substrate for ATP-binding cassette (ABC) transporters such as P-glycoprotein-mediated efflux, and its metabolism in humans mainly catalyzed by CYP 3A4 and 2C8. Genistein, an isoflavonoid, is supposed to be an inhibitor of some ABC transporters, and its oxidative metobolism catalyzed by CYP 3A4 and 2C8. The purpose of this study was to investigate the effect of orally administered genistein on the pharmacokinetics of paclitaxel administered through oral and intravenous (i.v.) route in rats. A single dose of paclitaxel administered orally (30 mg/kg) or i.v. (3 mg/kg) alone or 30 min after oral administration of genistein (3.3 mg/kg or 10 mg/kg). The presence of 10 mg/kg genistein significantly ($p < 0.05$) increased the area under the plasma concentration–time curve (AUC, 54.7% greater) of orally administered paclitaxel, which was due to the significantly ($p < 0.05$) decreased total plasma clearance (CL/F) of paclitaxel (35.2% lower). Genistein also increased the peak concentration (C_{max}) of paclitaxel significantly ($p < 0.05$ by 3.3 mg/kg, 66.8% higher; $p < 0.01$ by 10 mg/kg, 91.8% higher). Consequently, the absolute bioavailability (F) of paclitaxel in the presence of genistein was 0.020–0.025, which was elevated more than the control group (0.016); and the relative bioavailability (Fr) of orally administered paclitaxel was increased from 1.26- to 1.55-fold. Ten milligrams per kilogram genistein also significantly ($p < 0.05$) increased the AUC (40.5% greater) and reduced the total clearance (CLt, 30% lower) of i.v. administered paclitaxel.

The presence of genistein improved the systemic exposure of paclitaxel in this study. The pharmacokinetic interaction between them should be taken into consideration when paclitaxel is used with genistein or the dietary supplements full of genistein.

Keywords: Paclitaxel; Genistein; Pharmacokinetics; Bioavailability; Rats

1. Introduction

Paclitaxel (Taxol®) is an antineoplastic agent derived from the bark of the Pacific yew tree (*Taxus brevifolia*). Paclitaxel is primarily metabolized in the liver by CYP 3A4 and 2C8 and undergoes biliary excretion (Harris et al., 1994; Rahman et al., 1994; Sonnichsen et al., 1995). The fecal excretion level in humans approximates 70% of the administered paclitaxel dose, with 6α-hydroxypaclitaxel being the major metabolite (Walle et al., 1995). Orally administered paclitaxel presents a major therapeutic problem because of low bioavailability due to poor solubility and the first-pass metabolism that occurs in the liver and intestine. Therefore, paclitaxel is currently dissolved in a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol (1:1, v/v) for the intravenous (i.v.) dosage form. Cremophor EL, however, is itself toxic and causes vasodilatation, labored breathing, lethargy and hypotension (Rowinsky et al., 1993). When taken orally, paclitaxel is a substrate for P-glycoprotein (P-gp) efflux in the intestine. P-gp is a member of the ATP-binding cassette (ABC) superfamily (Sparreboom et al., 1997). Several studies have reported that the low bioavailability of paclitaxel following oral administration would result from metabolism by the enzymes or counter-transport processes due to P-gp in the intestinal wall. It was reported that when concomitantly administered with cyclosporine A (a P-gp and CYP 3A inhibitor) the oral bioavailability of paclitaxel was markedly higher than paclitaxel alone in human (Meerum Terwogt et al., 1999) and mice (van Asperen et al., 1998). Paclitaxel is also known to be a substrate for the efflux of other ABC superfamily members, such as BCRP (Doyle and Ross, 2003) and MRP2 (Huisman et al., 2005). The ABC family of transport proteins plays a central

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role in the defense of organism against toxic compounds and a diverse number of anticancer agents (Higgins, 1992; Borst et al., 2000). P-gp, MRP2 and BCRP located within the polarized apical membrane of the intestine, liver and kidney and mediate the efflux of xenobiotics and toxins into the intestinal lumen, bile and urine (Chan et al., 2004). Moreover, the MRPs and P-gp are co-localized with CYP3A4, glutathione-*S*-transferases and UDP-glucuronosyltransferases (Sutherland et al., 1993; Turgeon et al., 2001), which are thought to act synergistically in regulating the bioavailability of many orally ingested compounds.

The isoflavonoids, which include aglycones and their glucosides, are generally classified as phytoestrogens. The main isoflavones present in the diet of humans are genistein and daidzein from soybeans (Ren et al., 2001). Recently, these phytoestrogens have become available over-the-counter in the form of 'phytopharmaceuticals'. The consumption of an isoflavonoid-rich diet has been associated with a decrease in the incidence of some hormone-related cancers (e.g., breast and prostate cancer) (Kurzer and Xu, 1997; Birt et al., 2001; Yang et al., 2001). The glycoside of genistein, genistin, is rapidly hydrolyzed to genistein in the intestine, rapidly absorbed and undergoes extensive phase II metabolism via glucuronidation and sulfation in the small intestine (Liu and Hu, 2002). The oxidative metabolism of genistein, which forms 3′-OH-genistein, catalyzed mainly by CYP 1A2, and CYP 2C8 and CYP 3A4 also provide a minor contribution to its formation in human liver microsomes (Hu et al., 2003). Data from *in vitro* studies indicate that genistein competitively inhibits P-gp (Castro and Altenberg, 1997), BCRP (Zhang et al., 2004; Imai et al., 2004) and MRP2-mediated drug efflux *in vitro* (Jager et al., 1997).

Since this phytoestrogen has become readily available over-the-counter, it is possible that genistein products would be taken along with prescribed paclitaxel. The CYPs and ABC transporters in the intestine and the liver primarily affect the systemic exposure of paclitaxel. As an inhibitor of ABC transporters and a substrate of the same enzymes of paclitaxel, it might be possible that genistein would improve the bioavailability of paclitaxel. There is not any report about the pharmacokinetic interaction between paclitaxel and genistein. The purpose of this study was to investigate the effects of genistein on the pharmacokinetics of paclitaxel administered by two different routes in a rodent model.

2. Materials and methods

2.1. Materials

Paclitaxel was purchased from the Bristol-Myers Squibb Co. (NY, USA). Saline (0.9% NaCl injectable solution) was obtained from the Choongwae Co. (Seoul, Korea), acetonitrile, methanol and *tert*-butylmethylether were acquired from the Merck Co. (Darmstadt, Germany). Genistein and *n*-butyl p-hydroxybenzoate (butyl paraben) was purchased from the Sigma Chemical Co. (St. Louis, MO, USA) and phosphoric acid from the Junsei Co. (Tokyo, Japan). All other chemicals for this study were of reagent grade and were used without further purification.

A high performance liquid chromatograph (HPLC, Waters 1515 isocratic HPLC Pump, Waters 717 plus autosampler, Waters 2487 Dual λ absorbance detector, Waters Co., Milford, MA, USA), a sonicator (Bransonic Ultrasonic, CT, USA), a MG 2100 Eyela dry thermo bath (Rikakikai Co., Tokyo, Japan), a high-speed micro centrifuge (Hitachi Co., Tokyo, Japan), a Bransonic® Ultrasonic Cleaner (Branson Ultrasonic Corporation, Danbury, CT, USA), and a vortex-mixer (Scientific Industries Co., NY, USA) were used in this study.

2.2. Animal experiments and drug administration

The male Sprague–Dawley rats weighing 270–300 g were purchased from the Dae Han Laboratory Animal Research and Co. (Choongbuk, Korea), and were given free access to a standard No. 322-7-1 chow diet (Superfeed Co., Gangwon, Republic of Korea) and tap water. The rats were housed (four or five rats per cage) in laminar-flow cages maintained at a temperature of 22 ± 2 °C, and a relative humidity of 50–60%, under a 12:12 h light–dark cycle. The rats were kept under these conditions for at least one week before the experiment was initiated. The Animal Care Committee of Chosun University approved the protocol for this animal study. The animal care committee of Chosun University (Gwangju, Republic of Korea) approved the design and the conduct of this study.

The rats were divided into six groups containing six animals in each group: (1) an oral control group, administered 30 mg/kg of paclitaxel intragastrically (i.g.), which was i.g. pretreated with distilled water (∼1.0 ml/rat) 30 min before; (2 and 3) the oral pretreatment groups, genistein at the dose of 3.3 and 10 mg/kg i.g. pretreated 30 min before oral administration of paclitaxel, respectively; (4) an i.v. control group, i.v. administered 3 mg/kg of paclitaxel, which was i.g. pretreated with distilled water (∼1.0 ml/rat) 30 min before; (5 and 6) the i.v. pretreatment groups, genistein at the dose of 3.3 and 10 mg/kg i.g. pretreated 30 min before i.v. administration of paclitaxel.

The rats were fasted for at least 24 h before the beginning the experiments and had access to tap water *ad libitum*. The right femoral vein (for i.v. administration) and the femoral artery (for blood sampling) were cannulated with polyethylene tube (Clay Adams, Parsippany, NJ) under light ether anesthesia.

Paclitaxel solution was prepared by dissolving paclitaxel in a Cremophor EL and ethylalcohol mixture (1:1, v/v, 6 mg/ml for i.v. and 20 mg/ml for oral administration). Paclitaxel solution for i.v. administration was diluted with saline immediately and injected through the femoral vein within 40 s (∼0.5 ml/rat); the paclitaxel solution for oral administration was hand mixed with hydroxypropyl methylcellulose powder (50 mg/ml) to obtain a suspension and further diluted with distilled water (Gao et al., 2003) just before i.g. gavage (∼1.5 ml/rat). Genistein was suspended in distilled water (∼1.0 ml/rat) before i.g. gavage by vortex-mixing vigorously for over 30 min at 37 °C until genistein particles were invisible. Blood samples (0.6 ml) were collected into heparinized tubes from the femoral artery at 0 (to serve as a

control), 0.017 (only for i.v. administration), 0.1, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after paclitaxel administration, and centrifuged at 13,000 rpm for 5 min. The plasma samples stored at −40 °C until HPLC analysis.

2.3. HPLC analysis

The plasma concentrations of paclitaxel were determined using the HPLC method of Andreeva et al. (1997) and Lee et al. (1999) after a slight modification. Briefly, a 0.2 ml aliquot of plasma sample was mixed with a 50 μl aliquot of butyl paraben (4 μg/ml, internal standard), a 0.8 ml aliquot of *tert*-butylmethylether, and a 0.6 ml aliquot of a saturated dipotassium hydrogen phosphate solution in a 2.0 ml polypropylene microtube. It was then vortex-mixed vigorously for 0.5 min, centrifuged for 10 min at 13,000 rpm and a 0.6 ml aliquot of the upper layer carefully transferred to a clean microtube and evaporated under the gentle stream of nitrogen gas in a dry thermo bath at 38 °C. The resulting residue was dissolved in a 0.2 ml aliquot of 60% acetonitrile in deionized water and washed with a 1.0 ml aliquot of *n*-Hexane. A 50 μl aliquot of the solution was injected into HPLC for analysis.

The UV detector was operated at a wavelength of 227 nm. A Symmetry® C_{18} column (4.6 mm × 150 mm, 5 μm, Waters Co., Milford, MA, USA) was used at a temperature of 30 °C set by the HPLC column temperature controller (Phenomenex Inc., CA, USA). The mobile phase, acetonitrile–methanol–0.1%H_3PO_4 (45:12:43, v/v/v), was run at the flow rate of 1.3 ml/min. Chromatograms of blank plasma and plasma spiked with paclitaxel and butyl paraben are shown in Fig. 1. The peaks of paclitaxel and the butyl paraben were distinctly separated; the retention times of paclitaxel and butyl paraben were 6.7 and 4.8 min, respectively. The detection limit of paclitaxel was 10 ng/ml. The coefficient of variation was below 14.2%.

2.4. Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was performed using the LAGRAN computer program (Rocci and Jusko, 1983), which uses the LARGAN method to calculate the area under the plasma concentration–time curve (AUC) of plasma concentration (C_p) as a function of time (t). The peak plasma concentration (C_{max}) and the time to reach peak plasma concentration (T_{max}) were determined by a visual inspection of the data. The elimination rate constant (K_{el}) was calculated from the slope of the line using regression analysis, and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. Total plasma clearance (CL_t) was calculated by Dose/AUC. Absolute bioavailability was taken into consideration when clearance was determined for the oral route (CL/F). The absolute bioavailability (F) was calculated by $AUC_{oral}/AUC_{IV} \times Dose_{IV}/Dose_{oral}$, and the relative bioavailability (Fr) was estimated by $AUC_{pretreated}/AUC_{control}$.

2.5. Statistical analysis

All mean values are presented with their standard deviation (mean ± S.D.). The pharmacokinetic parameters were compared using a one-way ANOVA, followed by *a posteriori* testing with the use of the Dunnett correction. Differences were considered to be significant at a level of $p < 0.05$.

3. Results

The plasma concentration–time profiles of paclitaxel following i.v. administration of paclitaxel (3 mg/kg) in the presence of genistein were shown in Fig. 2, and the pharmacokinetic parameters are provided in Table 1. Ten milligrams per kilogram genistein significantly ($p < 0.05$) increased the area under the plasma concentration–time (AUC) of paclitaxel by 40.5%, and reduced the total plasma clearance (CL_t) of paclitaxel by

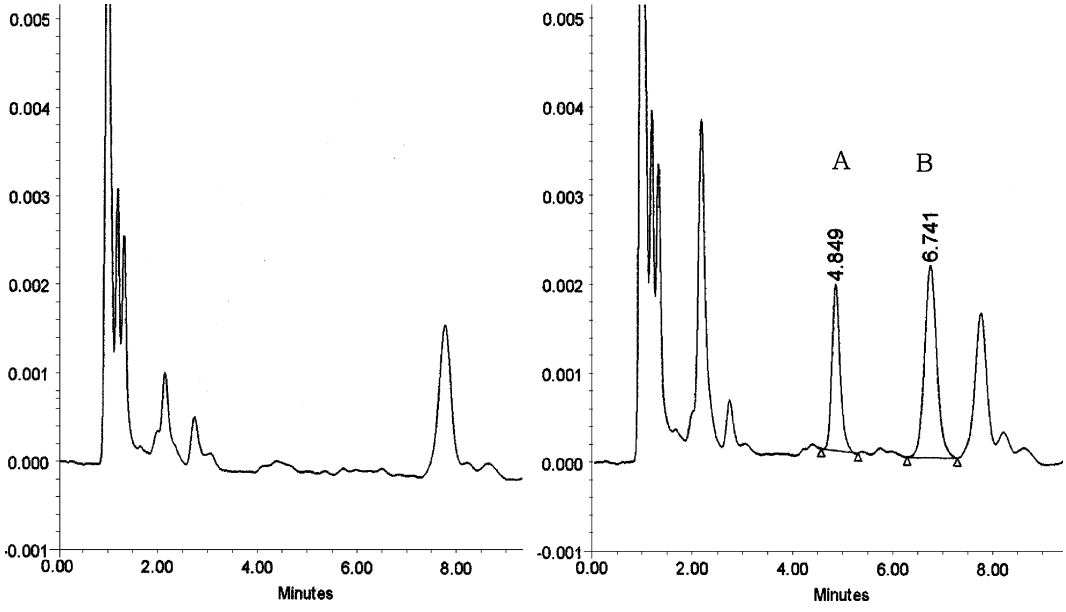

Fig. 1. Chromatograms of rat's blank plasma and the plasma spiked with paclitaxel (A, 6.7 min) and butylparaben (B, 4.8 min).

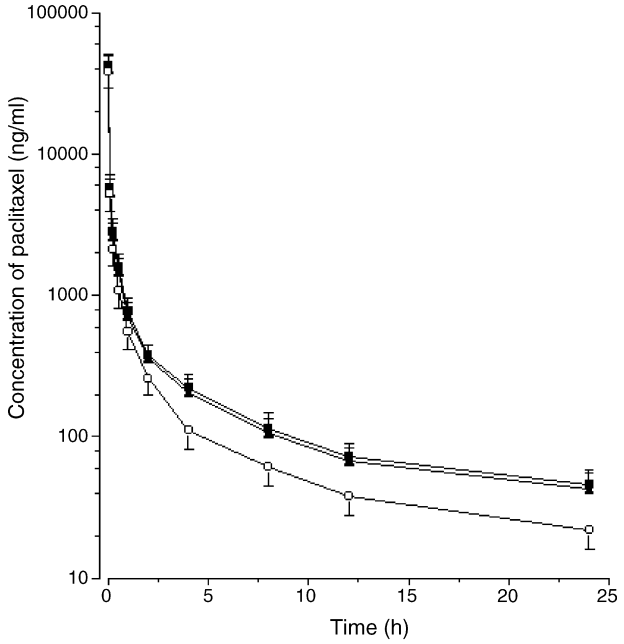

Fig. 2. Mean plasma concentration–time profiles of paclitaxel after i.v. administration of paclitaxel (3 mg/kg) to rats in the presence or absence of genistein. Bars represent the standard deviation (n = 6). (◯), i.v. administration of paclitaxel at a dose of 3 mg/kg; (▲), in the presence of genistein at a dose of 3.3 mg/kg; (■), in the presence of genistein at a dose of 10 mg/kg.

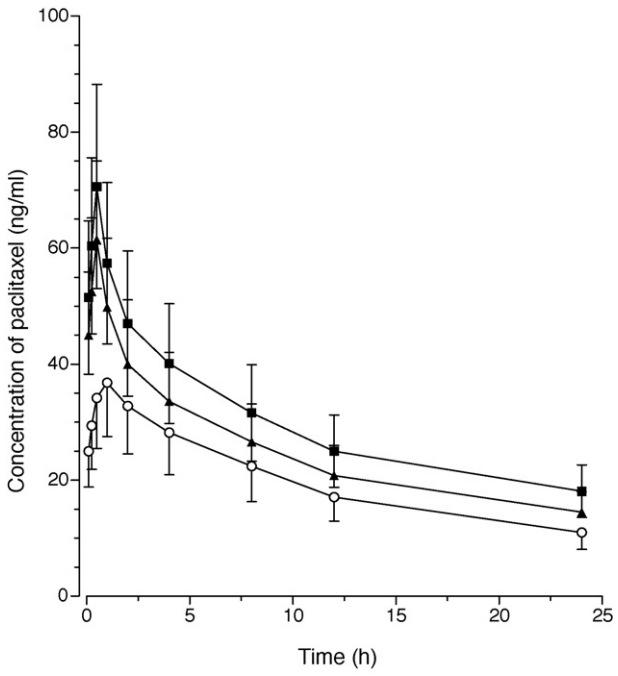

Fig. 3. Mean plasma concentration–time curves of paclitaxel after oral administration of paclitaxel (30 mg/kg) to rats in the presence or absence of genistein (3.3 and 10 mg/kg). Bars represent the standard deviation (n = 6). (◯), oral administration of paclitaxel at a dose of 30 mg/kg; (▲), in the presence of genistein at a dose of 3.3 mg/kg; (■), in the presence of genistein at a dose of 10 mg/kg.

30%. Other pharmacokinetic parameters were not altered significantly such as the elimination rate constant (K_{el}) and the terminal half-life ($t_{1/2}$) of paclitaxel. Although 3.3 mg/kg genistein also increased the AUC and decreased the CL_t of paclitaxel, they have not shown statistic difference ($p > 0.05$).

The plasma concentration–time profiles of paclitaxel after oral (30 mg/kg) administration in the presence or absence of genistein (3.3 and 10 mg/kg) were illustrated in Fig. 3, and the pharmacokinetic parameters for paclitaxel were shown in Table 2. The presence of 10 mg/kg genistein significantly ($p < 0.05$) increased the AUC (54.7% greater) of paclitaxel, and significantly ($p < 0.05$) decreased the total plasma clearance (CL/*F*) of paclitaxel (35.2% lower). Although 3.3 mg/kg genistein also increased AUC of paclitaxel by 26.1%, it was not statistically significant ($p > 0.05$). Genistein also increased the peak plasma concentration (C_{max}) of paclitaxel significantly ($p < 0.05$ by 3.3 mg/kg, 66.8% higher; $p < 0.01$ by 10 mg/kg, 91.8% higher). Consequently, the absolute bioavailability (*F*) of paclitaxel which was 0.016 in the oral control group was elevated from 0.020 to 0.025, and the relative bioavailability (Fr) of paclitaxel was increased from 1.26- to 1.55-fold. No statistical differences of K_{el} and $t_{1/2}$ of paclitaxel were observed in the presence of genistein ($p > 0.05$).

Table 1
Mean (±S.D.) pharmacokinetic parameters of paclitaxel after i.v. administration of paclitaxel (3 mg/kg) to rats in the presence or absence of genistein

Parameters	Control	Paclitaxel + genistein	
		3.3 mg/kg	10 mg/kg
AUC (ng h ml^{-1})	4431 ± 1024	5870 ± 1421	6325 ± 1437*
CL_t (ml min^{-1} kg^{-1})	11.3 ± 2.91	8.51 ± 2.13	7.91 ± 1.98*
K_{el} (h^{-1})	0.075 ± 0.017	0.070 ± 0.015	0.068 ± 0.014
$t_{1/2}$ (h)	9.24 ± 2.43	9.91 ± 2.51	10.19 ± 2.69
Fr	1.00	1.32	1.41

Mean ± S.D. ($n = 6$), $^{*}p < 0.05$ compared to control. AUC: area under the plasma concentration–time curve from 0 h to infinity; K_{el}: elimination rate constant; MRT: mean residence time; Fr: relative bioavailability.

Table 2
Mean (± S.D.) pharmacokinetic parameters of paclitaxel after oral administration of paclitaxel (30 mg/kg) to rat in the presence or absence of genistein

Parameters	Control	Paclitaxel + genistein	
		3.3 mg/kg	10 mg/kg
AUC (ng h ml^{-1})	702 ± 184	885 ± 213	1086 ± 249*
CL/*F* (ml min^{-1} kg^{-1})	712 ± 186	560 ± 143	461 ± 115*
C_{max} (ng/ml)	36.8 ± 9.5	61.4 ± 15.5*	70.6 ± 18.0**
T_{max} (h)	1.0	0.5	0.5
K_{el} (h^{-1})	0.047 ± 0.012	0.045 ± 0.011	0.043 ± 0.109
$t_{1/2}$ (h)	14.7 ± 3.71	15.4 ± 3.83	16.2 ± 4.01
F	0.016	0.020	0.025
Fr	1	1.26	1.55

Mean ± S.D. ($n = 6$), $^{*}p < 0.05$, $^{**}p < 0.01$ compared to control. AUC: area under the plasma concentration–time curve from 0 h to infinity; CL/*F*: total plasma clearance; C_{max}: peak concentration; T_{max}: time to reach peak concentration; K_{el}: elimination rate constant; $t_{1/2}$: terminal half-life; *F*: absolute bioavailability; Fr: relative bioavailability.

4. Discussion

Paclitaxel metabolism is catalyzed mainly by CYP 3A4 and 2C8 (Harris et al., 1994; Rahman et al., 1994; Sonnichsen et al.,

1995), and it is a substrate for the efflux transporters such as P-gp (Sparreboom et al., 1997), BCRP (Doyle and Ross, 2003) and MRP2 (Huisman et al., 2005). Inhibition of the metabolic enzymes and the efflux transporters must be the contributors to improve the systemic exposure of paclitaxel.

As shown in Table 1, the presence of genistein at a dose of 10 mg/kg significantly increased the AUC and reduced CL_t of i.v. administered paclitaxel. Since genistein not only subjects to CYP2C8 and 3A4 mediated metabolism (Hu et al., 2003) but also provide inhibition of P-gp, BCRP and MRP2 efflux function, the decreased CL_t and increased AUC of etoposide suggests the metabolism and excretion of paclitaxel in the liver and kidney might be inhibited. This study is consistent with the results reported by Lim and Choi (2006) in that naringin, a dual inhibitor of CYP3A and P-gp, significantly increased the AUC and reduced the CL_t of i.v. administered paclitaxel in rats.

The presence of genistein at a dose of 10 mg/kg also increased the AUC and reduced the CL/*F* of orally administered paclitaxel (Table 2). Walle et al. (1995) reported that after i.v. administration of paclitaxel the total fecal excretion was 71.1% with 6α-hydroxytaxol being the major component, and the total urinary excretion was only 14.3% of the dose with parent form as the main excretion products, which suggests paclitaxel mainly excreted as the metabolite via the liver. As shown in Tables 1 and 2, the $t_{1/2}$ of orally administered paclitaxel prolonged almost 1.6-fold compared to i.v. routes, and the *F* values is only 0.016 in oral control group, which indicates that orally administered paclitaxel might subject to extensive first-pass metabolism and enteric and interohepatic circulation. The increased AUC and reduced CL/*F* of paclitaxel might be mainly due to the inhibited CYP3A and P-gp, which are located in the intestine and liver. It could be supported by the reports in that quercetin, a dual inhibitor of P-gp and CYP 3A4, enhanced oral bioavailability of paclitaxel (Choi et al., 2004a) and cyclosporine, a substrate of P-gp and CYP 3A4 (Choi et al., 2004b). van Asperen et al. (1998) also reported that concomitant administration of cyclosporine A, an inhibitor of CYP3A and P-gp, significantly increased the oral bioavailability of paclitaxel in mice, which was confirmed in humans as well (Meerum Terwogt et al., 1999). The presence of genistein at a dose of 3.3 mg/kg also increased the AUC and decreased the CL_t (or CL/*F*) of orally and i.v. administered genistein, but they were not significant compared to their control groups. Genistein presents the dose-dependent inhibition of the efflux of paclitaxel and vinblastine in KB-V1 cells highly expressing P-gp (Limtrakul et al., 2005). The systemic concentration of orally administered genistein at a dose of 3.3 mg/kg might be not high enough to exert its inhibition of P-gp and CYPs sufficiently.

Several chemicals such as verapamil, cyclosporine A and PSC 833 have been proved to be the potent P-gp inhibitors in vitro, but their toxicities have hindered their use as the multi-drug resistance (MDR) modulators in the clinical practice (Bradshaw and Arceci, 2000). Since genistein is reported non-toxic and has many health-benificial activity, it might be a good candidate of MDR modulator in improving the bioavailability of paclitaxel. Further study is needed in the anticancer therapy to demonstrate the potency of genistein on the pharmacokinetics of paclitaxel in humans.

5. Conclusion

The presence of genistein enhanced the systemic exposure of paclitaxel in this animal study. Since this phytoestrogen has become available as an over-the-counter product, genistein is likely to be taken along with paclitaxel. Dosage regimen should take into consideration to avoid the toxic reaction by combination.

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