6

Pharmacokinetic Interactions of Antihypertensive Drugs with Citrus Juices

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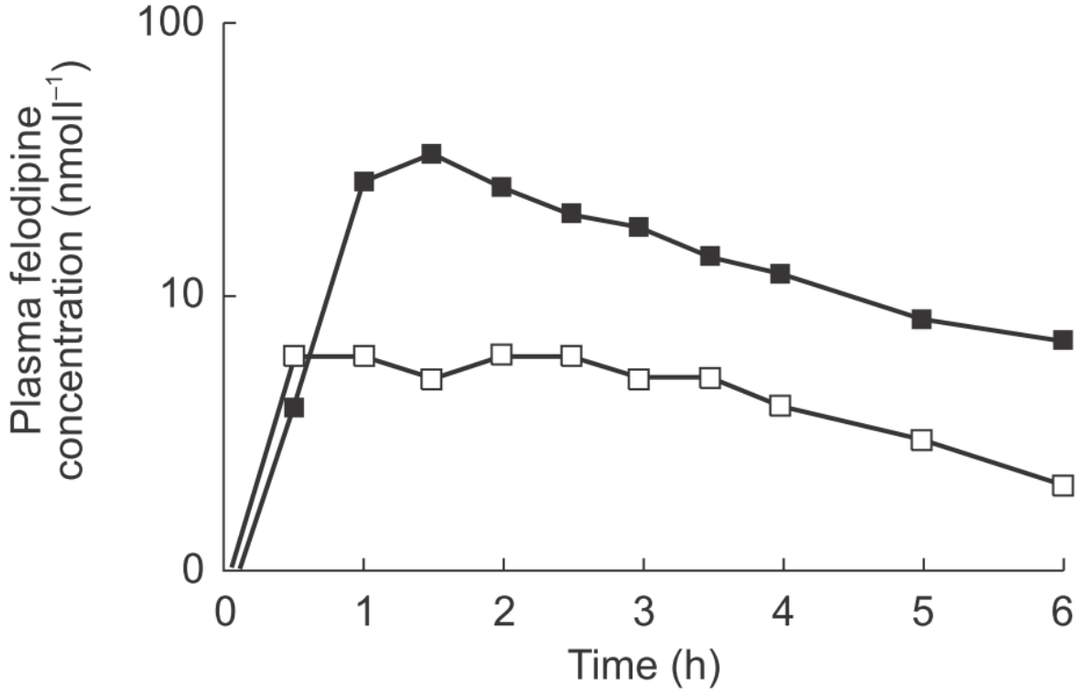
1. Introduction

It has been known that citrus juices cause pharmaceutical interactions with various kinds of medications. The citrus juice interactions are broadly divided into 2 types which are with increasing and decreasing of drug concentrations in plasma. That is, both types are categorized into pharmacokinetic interactions. In the "increasing" type interactions, grapefruit juice is the most important in the juices. Grapefruit juice makes an increase in the plasma drug concentrations due to the suppression of intestinal metabolization of the drugs. Since the danger of concomitant administration of drugs and grapefruit juice was discovered in 1989, drinking of the juice has been controlled in patients undergoing pharmaceutical therapies. The targeted medications for the restriction ranges from antilipemics to immunosuppressants. Antihypertensive drugs are one of the typical categories of drugs affected by such interaction. A feature of said drugs is that they are characterized as substrates of Cytochrome P-450 3A, the most important-drug metabolizing enzyme in the intestines. Dihydropyridine calcium channel antagonists, as well as verapamil in the antihypertensive drugs was representative of drug categories with such property. In this chapter, grapefruit juice interactions were described, and the latest knowledge presented, as a results of research utilizing statistical investigations with dihydropyridines. On the other hand, information about the "decreasing" type of interactions has been reported in a limited number of research results. Some clinical studies related to β-adrenergic-blocking agents (antihypertensives) such as celiprolol as well as fexofenadine (antihistamine), it was discovered that citrus juices such as orange juice and grapefruit juice reduce intestinal absorption of the drugs. In this chapter, results of the studies of the interactions are explained; and the research attributing an important ingredient in orange juice in the interaction with the β-blocker, is described.

2. Grapefruit juice interactions related to the increase of plasma drug concentrations

In 1989, Bailey and colleagues used grapefruit juice (GFJ) to mask the taste of alcohol in a clinical trial of the interaction between alcohol and drugs. They found that plasma felodipine levels were higher in subjects given GFJ (Bailey, 1989); and in 1991, they published a similar work on both felodipine and nifedipine (Bailey, 1991). At present, GFJ must be avoided in patients receiving certain drugs to prevent this interaction (Figure 1).



Felodipine 5 mg tablet was administered with 350 mL double-strength GFJ (black squares) or water (white squares). This figure was cited from the literature (Bailey, 1998)

Fig. 1. Plasma felodipine concentration-time profile.

2.1 Antihypertensive drugs related with the GFJ- interactions

Concomitant administration of GFJ with a variety of drugs including antihypertensive drugs results in enhancement of plasma concentrations of the drugs. The first example of a GFJ interaction was an increase in levels of the dihydropyridine calcium channel antagonists, felodipine and nifedipine (Bailey et al., 1991), but at least 13 drugs in this category also interact with GFJ: amlodipine (Josefsson, 1996), azelnidipine (Hirashima, 2006), benidipine (Ohnishi, 2006), cilnidipine (Ohnishi et al., 2006), efonidipine (Yajima, 2003), felodipine (Bailey et al., 1991), manidipine (Sugawara, 1996), nicardipine (Uno, 2000), nifedipine (Bailey et al., 1991), nimodipine (Fuhr, 1998), nisoldipine (Bailey, 1993b), nitrendipine (Soons, 1991), and pranidipine (Hashimoto, 1998). GFJ can interact with other diverse medicines such as verapamil (Ho, 2000) (calcium channel antagonist), simvastatin (Lilja, 1998) (HMG-CoA reductase inhibitor), and losartan (Zaidenstein, 2001) (angiotensin II receptor blocker).

2.2 The mechanism of GFJ-drug interactions

Most interacting drugs are substrates of Cytochrome P-450 3A (CYP3A). CYP3A is an important drug oxidation enzyme in human liver and the small intestine, and metabolizes 50% of commercially available drugs. CYP3A blocks the intestinal absorption of small-molecule xenobiotics from drugs and food and drink components. GFJ is a suicidal substrate of this enzyme (Lown, 1997; Schmiedlin-Ren, 1997). A single glassful of GFJ can decrease CYP3A activity by 47% (Lown et al., 1997), drastically increasing the fractional absorption of CYP3A substrates depending on other drug properties.

2.3 GFJ components involved in drug interactions

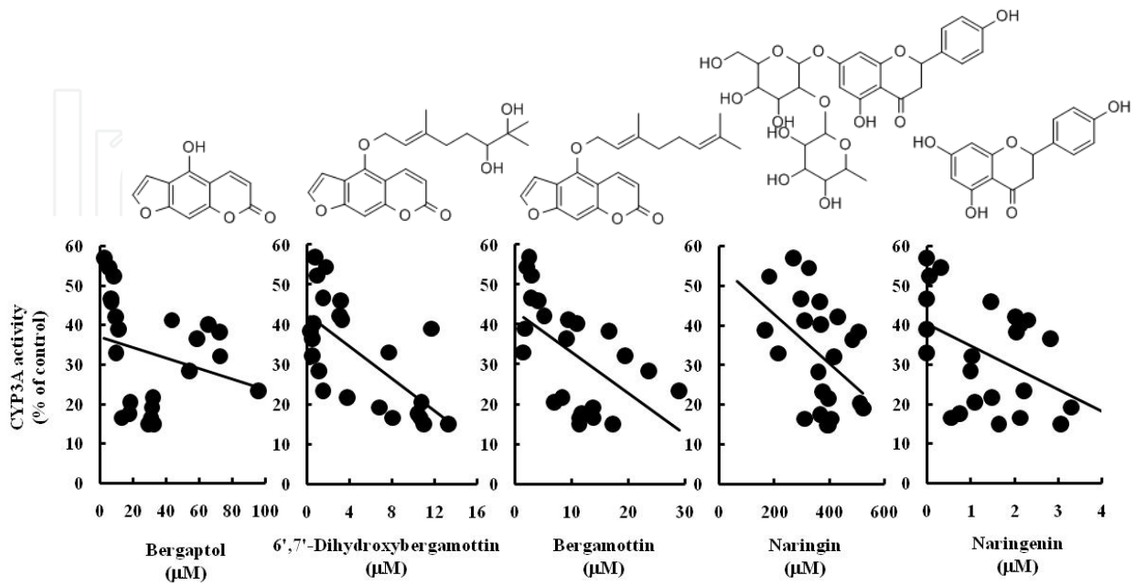
2.3.1 Construction of the estimation model on the CYP3A inhibitory effect of GFJ

When first discovered, naringin (NG), a high concentration ingredient in GFJ (Kane & Lipsky, 2000), and naringenin, an aglycone of naringin, were considered as the candidates that are most responsible for the interactions (Guengerich & Kim, 1990; Fuhr, 1993). The discovery of these components indicated CYP3A inhibition in *in vitro* experiments (Guengerich & Kim, 1990). However, studies on treatments with drugs combined with NG revealed that it does not contribute to the interactions (Bailey, 1993a). Currently, furanocoumarin derivatives such as bergamottin (BG) (He, 1998; Eagling, 1999; Malhotra, 2001; Mohri & Uesawa, 2001a; Goosen, 2004; Paine, 2004; Girennavar, 2006), 6′,7′-dihydroxybergamottin (DHB) (Eagling et al., 1999; Malhotra et al., 2001; Paine et al., 2004; Girennavar et al., 2006), and paradisins (Tassaneeyakul, 2000; Girennavar et al., 2006) are putative ingredients implicated in the interactions. The enzymatic inhibitory effects of these ingredients have been studied. However, the contributing rate of each derivative in the pharmaceutical interaction or CYP3A inhibitory effect was still being debated.

Estimation of the amount of contribution to the inhibitory effect by the purified ingredients might be difficult because concentrations of the furanocoumarins in GFJ vary with the brand of juice (Uesawa, 2008; Uesawa & Mohri, 2008b). While it is considered that estimation of the interaction potential on each GFJ brand is useful to select drinkable brands for patients undergoing pharmaceutical treatment, the complexity of interactive mechanisms with plural causative ingredients makes such estimation difficult. Therefore, we investigated the relationships between CYP3A inhibitory effects in a variety of GFJs and the concentrations of the ingredients, to construct a prediction model for the interaction potentials of GFJ (Uesawa, 2011a). Concentrations of bergaptol (BT), BG, DHB, NG, and naringenin in 23 kinds of GFJ were determined with high-performance liquid chromatography (HPLC) systems, equipped with photodiode array and electrospray ionization mass spectrometric detectors. Furthermore, inhibitory effects on CYP3A activity were measured based on the initial rate for testosterone 6β-hydroxylation in the presence of each GFJ. The concentrations of bergaptol, DHB, BG, NG, and naringenin in GFJ used in this study were 31.6, 4.97, 10.4, 364, and 1.37 μM, respectively. Addition of the juice to the reaction mixtures reduced human CYP3A activities to 32.7 % of the control. The residual activities underwent a multitude of changes, depending on the GFJ sample. The relationship between the concentration of 5 kinds of ingredients present in GFJ and their residual activities on CYP3A were studied to investigate the cause of the variability.

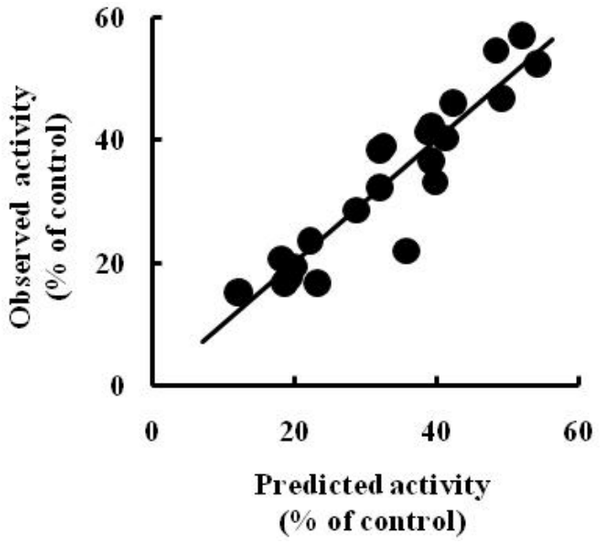
Figure 2 shows stacker plots between bergaptol, DHB, BG, NG, and naringenin concentrations, and the remaining CYP3A activities in the 23 kinds of GFJ. All the ingredients except bergaptol showed significant negative relationships for the residual activities. Multiple linear regression analysis was performed to estimate the contribution ratios of the GFJ-ingredients to the inhibitory effects on CYP3A activity. A multiple regression model where concentrations of DHB, BG, and NG were used as the significant variables was constructed (Figure 3). The inhibitory effects of GFJ on CYP3A activities could be attributed to almost all these ingredients because the contribution ratio in the above equation was 88% (Figure 3). Standardized partial regression coefficients of DHB, BG, and NG suggest that the order of contribution of the ingredients in the whole juice to the CYP3A inhibition is in the order of DHB>BG>>NG. We believe that the furanocoumarins including DHB and BG were important factors in the GFJ

interactions, compared with the other components such as flavonoid. Our findings suggest that quantitative determination of DHB and BG was a useful method for brief assessment of GFJ brands in pharmaceutical interactions.



This figure was cited from the literature (Uesawa et al., 2011a).

Fig. 2. Plots of concentrations of ingredients vs. observed CYP3A activities (% of control) with 23 kinds of GFJ.



Activity = 65.5 - 2.18DHB - 0.936BG - 0.0338NG (R^2 = 0.875)
In the equation, "activity" indicates the remaining CYP3A activity in the reaction mixture added to each GFJ. "DHB", "BG", and "NG" indicate the respective concentrations (μM) in each GFJ.
This figure was cited from the literature (Uesawa et al., 2011a).

Fig. 3. Multiple linear regression between predicted and observed CYP3A activities (% of control) with 23 kinds of GFJ.

2.3.2 QSAR analysis of the inhibitory effects of furanocoumarin derivatives on CYP3A activities

Furanocoumarin derivatives (FCs) exist in citrus fruits such as lime (Saita, 2004) and pomelo (Uesawa & Mohri, 2005) and umbellifers (Fujioka, 1999) as well as grapefruit. Like grapefruit, foods, drinks, and medicines from these plants might affect drug absorption. In fact, it was reported that pomelo juice, which has 8 kinds of FCs (Uesawa & Mohri, 2005), increased the bioavailability of cyclosporine A (Grenier, 2006). In one article, IC_{50} values of a variety of FCs on testosterone-6-ß hydroxylation were evaluated using human liver microsomes as the inhibitory effects (Guo, 2000). However, some points were still unclear regarding the relationship between the CYP-inhibitory effects and physicochemical profiles of FCs. Therefore, the quantitative structure-activity relationship (QSAR) study on the CYP3A inhibitory effects of FCs was designed such that the structural, physicochemical, and quantum chemical properties on FCs can be elucidated by use of computational chemical predictions (Uesawa & Mohri, 2010). Common logarithmic IC_{50} values of human liver microsomal testosterone 6-ß-hydroxylations were configured as objective variables. A variety of structural, physicochemical, and quantum chemical descriptors were computed from 2D and optimized 3D structures in the 37 FCs (Figure 4) as explanatory variables. Simple and multiple linear regression analyses were used to evaluate these parameters. IC_{50} values were taken from the literature and used as parameters that indicate the CYP3A inhibitory effect of the 37 kinds of FCs (Guo et al., 2000). Common logarithms of the parameters (log IC_{50}) were utilized as objective variables in the present regression analyses.

We attempted to construct multiple regression equations using descriptors and their square values that were calculated in this study. As a result, the best model was a quadratic function with log P and log P^2 (Figure 5).

The final model is

$$\text{Log } IC_{50}=1.44-0.385\text{AlogP}+0.0528(\text{AlogP}-4.00)^2$$

Variation of log IC_{50} values was interpretable in log P because the contribution ratio of the regression model constructed from log P was 81.2% for 36 FCs except FC24 (bergamottin). The presence of an outlier on bergamottin suggests that unknown physicochemical properties might differentiate the inhibitory effects of bergamottin from that of the other FCs. The structural characteristics of bergamottin are difficult to distinguish from those of the other FCs such as FC25, FC26, and FC27 with log P values close to that of bergamottin. On the other hand, we have reported that an effect of bergamottin on nifedipine oxidation activity with rat-liver microsomes was greater than those of FC26 (6′,7′-dihydroxybergamottin), FC2 (bergapten), and bergaptol (Mohri & Uesawa, 2001a). Herein, logP values of 6′,7′-dihydroxybergamottin, bergapten and bergaptol, 3.41, 2.19 and 1.94, respectively, were lower than bergamottin's 5.48. This order of inhibitory effects of the FCs also perfectly correlates with the order from the model equation. In the model, the IC_{50} value of bergamottin was estimated at 280nM. In fact, it became evident that bergamottin is one component involved in the GFJ-drug interaction that results in inhibition of the CYP3A enzyme in the intestinal lumen *in vivo* (Goosen et al., 2004). Goosen et al. reported significant increase in felodipine AUC, area under the plasma concentration-time curve, when subjects co-administered bergamottin at the same concentration of GFJ. These findings and our estimation from the regression model suggest that bergamottin could be an important factor in GFJ-interactions.

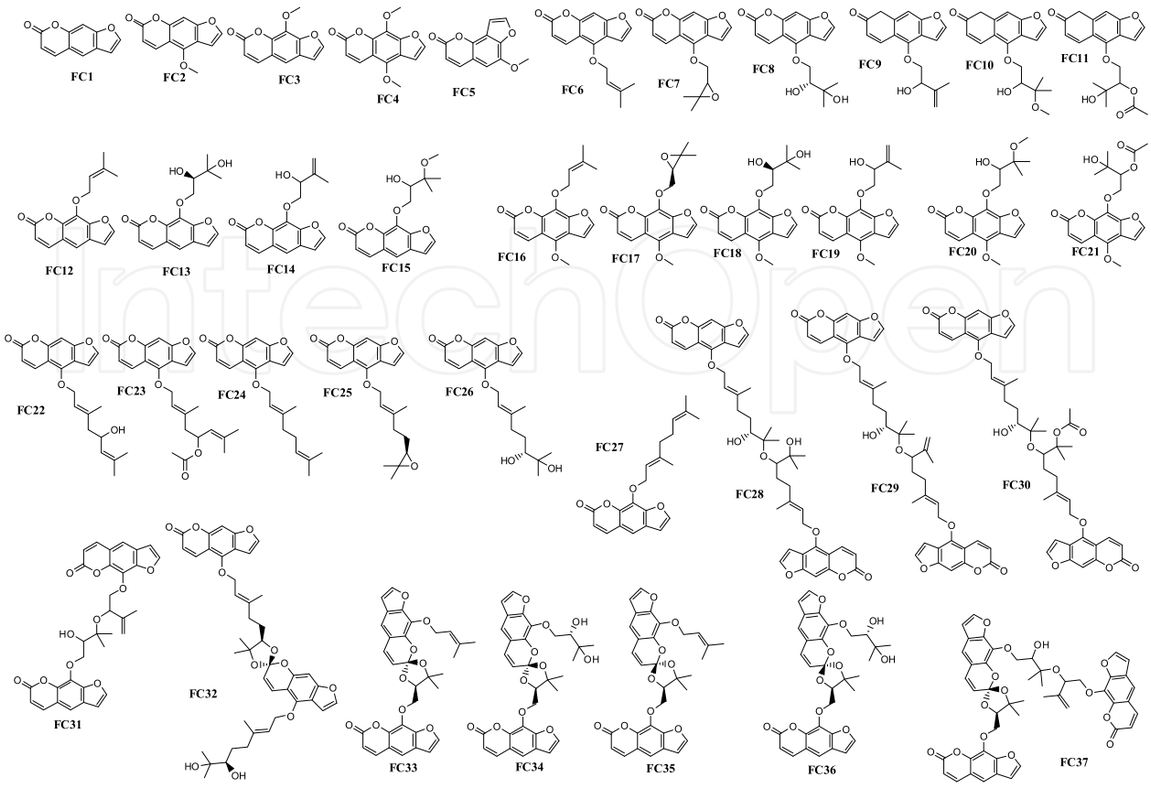
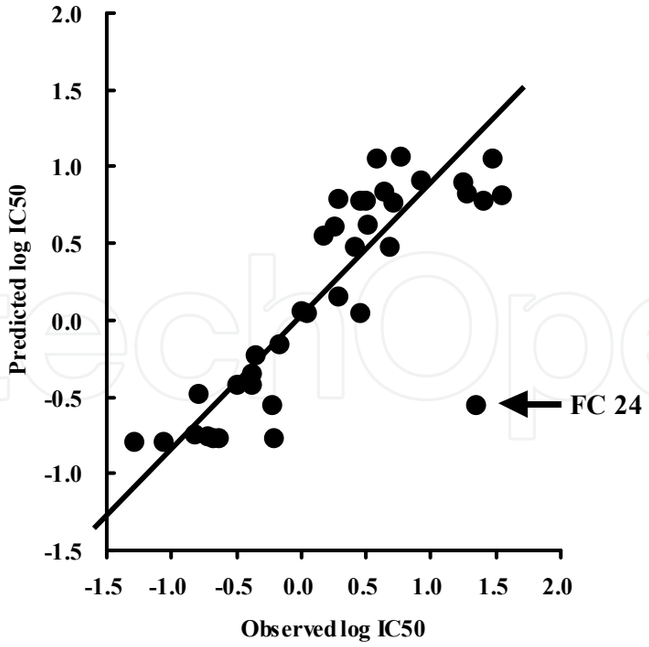


Fig. 4. Chemical structures of FCs.



This figure was cited from the literature (Uesawa & Mohri, 2010)

Fig. 5. Linear regression between predicted and observed values of IC_{50} in CYP3A activities of FCs obtained in the model with AlogP and $AlogP^2$.

2.4 Meta-analyses of studies of GFJ interactions with dihydropyridine drugs

Studies on GFJ interaction are known to vary widely. We believed that studies with such a wide deviation should be integrated (Uesawa, 2011b). Amlodipine, efonidipine, manidipine, felodipine, nifedipine, and nisoldipine were mentioned in 2 reports (Josefsson et al., 1996; Vincent, 2000), 3 reports (Mimura, 1998, 2000; Yajima et al., 2003), 2 reports (Sugawara, 1996; Uno, 2006), 12 reports (Bailey et al., 1991, 1993a, 1998; Edgar, 1992; Bailey, 1995, 1996, 2000, 2003; Lundahl, 1995, 1997; Lown et al., 1997; Goosen et al., 2004), 6 reports (Bailey et al., 1991, 1993a; Rashid, 1993, 1995; Sigusch, 1994; Azuma, 1996; Ohtani, 2002), and 4 reports (Bailey et al., 1993a, b; Azuma et al., 1996; Takanaga, 2000; Ohtani et al., 2002), respectively (Table 1). Therefore, the GFJ interaction of each drug in these reports was set up as a target of the meta-analysis. In most of the reports on all drugs analyzed in this study, concomitant administration of GFJ resulted in the increment of concentrations and AUCs on the drugs in plasma compared with that of the control groups. There are some reports without significant increase in AUC for 3 kinds of dihydropyridine drugs, namely, efonidipine, nifedipine, and amlodipine with concomitant intake of GFJ (Figure 7, 8, and 12). There were significant increases in AUCs in the groups that administered GFJ compared with those that administered water for efonidipine, felodipine, nifedipine, manidipine, and nisoldipine (Figure 7-11). On the other hand, a meta-analysis of amlodipine showed no significant interaction (Figure 12). All other single studies on azelnidipine, benidipine, cilnidipine, nicardipine, nimodipine, nitrendipine, and pranidipine showed significant increases in AUCs in the groups that administered GFJ, compared with the control groups. Amlodipine was considered the only safe medication among all the dihydropyridine drugs reported to date. The numbers of studies for manidipine, amlodipine and efonidipine are 2, 2, and 3, respectively. The quality of the results of meta-analyses based on these dihydropyridines might not be sufficient. Progress of additional studies is expected.

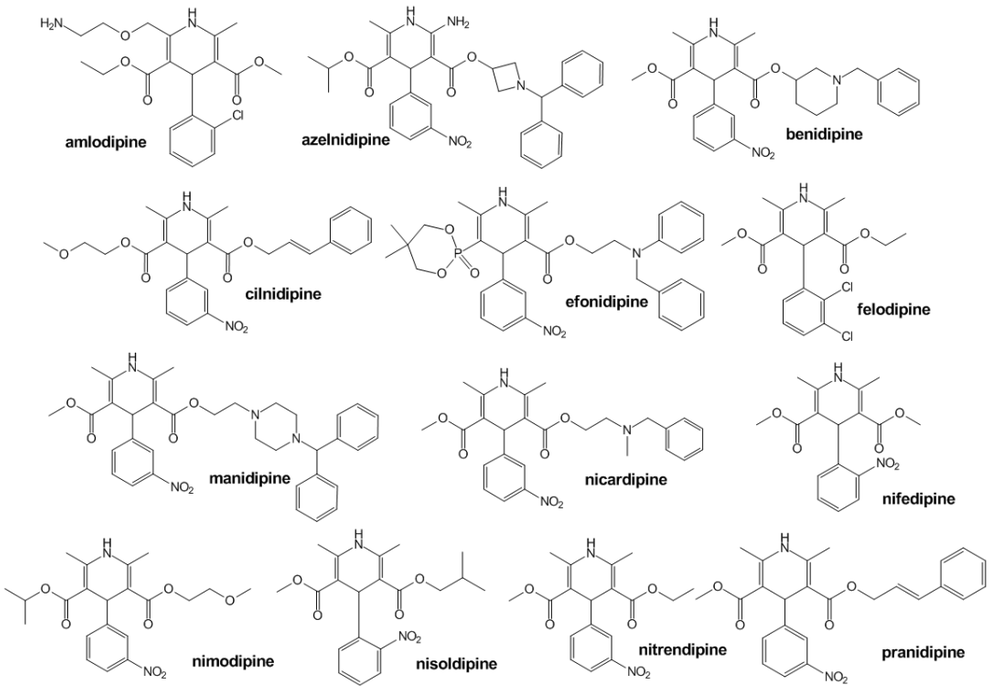
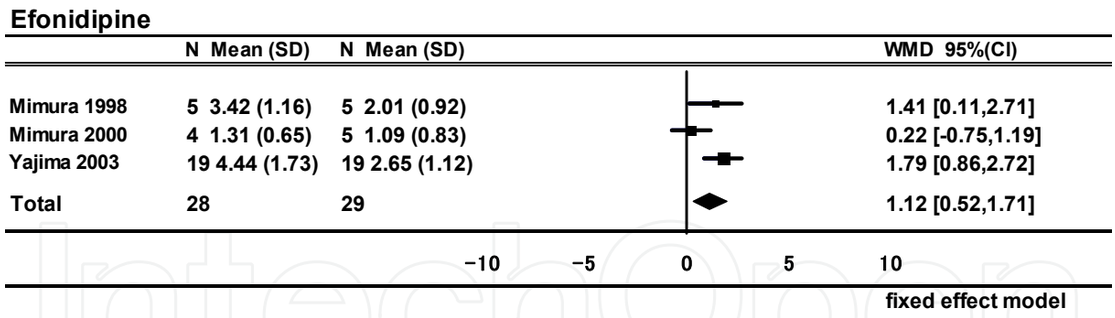


Fig. 6. Chemical structures of dihydropyridines.

				GFJ-administration						Control				
Drug	Author	Publication year	Jadad	n	Dose (mg)	GFJ (mL)	AUC (nmol x h/L/mg)		mean AUC	n	Dose (mg)	AUC (nmol x h/L/mg)		mean AUC	mean AUC ratio
amlodipine	Josefsson	1996	3	12	5	250	70.44	± 18.59	74.56	12	5	61.63	± 14.67	67.90	1.10
amlodipine	Vincent	2000	3	20	10	240	77.04	± 18.59		20	10	71.66	± 14.19		
azelnidipine	Hirashima	2006	2	8	8	250	31.73	± 9.41	31.73	8	8	9.68	± 2.01	9.68	3.28
benidipine	Coniel	1995	0	6	4	200	1.57		1.57	6	4	0.98		0.98	1.59
cilnidipine	Watanabe	1999	0	6	10	200	25.69		25.69	6	10	11.31		11.31	2.27
efonidipine	Mimura	1998	1	5	20	200	3.42	± 1.16	3.81	5	20	2.01	± 0.92	2.27	1.68
efonidipine	Mimura	2000	1	4	20	250	1.31	± 0.65		5	20	1.09	± 0.83		
efonidipine	Yajima	2003	2	19	40	250	4.44	± 1.73		19	40	2.65	± 1.12		
felodipine	Bailey	1991	3	6	5	500	20.60	± 7.35	11.20	6	5	8.20	± 3.92	5.76	1.94
felodipine	Edgar	1992	3	9	5	200	13.00	± 5.26		9	5	4.56	± 2.12		
felodipine	Bailey	1993	3	9	5	200	8.20	± 3.60		9	5	4.40	± 2.40		
felodipine	Bailey	1995	3	12	10	250	14.73	± 5.70		12	10	7.31	± 2.99		
felodipine	Lundahl	1995	3	9	10	200	14.59	± 3.03		9	10	10.17	± 2.12		
felodipine	Bailey	1996	3	12	10	250	12.93	± 3.79		12	10	6.71	± 3.07		
felodipine	Lown	1997	1	10	10	237	7.64	± 1.56		10	10	3.53	± 2.16		
felodipine	Lundahl	1997	3	12	10	150	11.50	± 3.53		12	10	6.68	± 2.08		
felodipine	Bailey	1998	3	12	10	250	13.00	± 5.20		12	10	5.30	± 2.42		
felodipine	Bailey	2000	3	12	10	250	5.40	± 2.77		12	10	2.50	± 1.73		
felodipine	Bailey	2003	2	8	10	250	6.50	± 3.11		8	10	3.60	± 2.26		
felodipine	Goosen	2004	3	11	5	250	9.20	± 2.56		11	5	6.82	± 2.04		
manidipine	Sugawara	1996	0	6	40		2.92	± 1.16	3.35	6	40	1.24	± 0.21	1.33	2.51
manidipine	Uno	2006	2	7	40	250	3.71	± 1.20		7	40	1.42	± 0.30		
nicardipine	Uno	2000	2	6	40	300	21.04	± 7.40	21.04	6	40	13.47	± 2.58	13.47	1.56
nifedipine	Bailey	1991	3	6	10	500	62.70	± 37.23	76.13	6	10	46.40	± 22.54	57.54	1.32
nifedipine	Rashid	1993	3	8	10	400	92.40	± 48.96		8	10	62.95	± 30.00		
nifedipine	Sigusch	1994	3	10	20	200	47.35	± 20.79		10	20	23.39	± 12.13		
nifedipine	Rashid	1995	3	8	10	400	86.91	± 27.43		8	10	55.15	± 17.04		
nifedipine	Azuma	1996	3	8	20	250	101.12	± 64.72		8	20	109.78	± 104.77		
nifedipine	Ohtani	2002	1	8	20	227	70.14	± 19.13		8	20	53.35	± 12.04		
nimodipine	Fuhr	1998	2	8	30	250	117.78	± 1.92	117.78	8	30	77.84	± 1.61	77.84	1.51
nisoldipine	Bailey	1993	3	12	20	250	4.51	± 2.50	5.48	12	20	2.56	± 0.94	2.24	2.45
nisoldipine	Azuma	1996	3	8	10	250	6.59	± 2.19		8	10	1.85	± 1.74		
nisoldipine	Takanaga	2000	1	8	5	200	8.26	± 3.35		8	10	2.01	± 0.80		
nisoldipine	Ohtani	2002	1	8	10	227	3.05	± 0.79		8	10	2.37	± 0.97		
nitrendipine	Soon	1991	3	9	20	150	9.95	± 8.77	9.95	9	20	4.41	± 2.75	4.41	2.25
Pranidipine	Hashimoto	1998	1	8	2	250	39.70	± 17.43	39.70	8	2	23.59	± 13.29	23.59	1.68

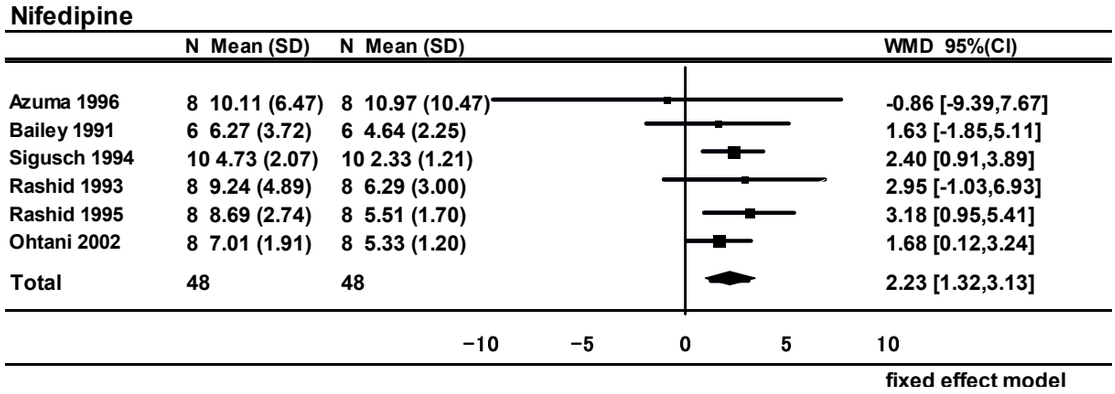
Volume of double strength GFJ was converted to that of single strength GFJ. The method for calculating mean AUC is described in Methods. This table was cited from the literature (Uesawa et al., 2011b).

Table 1. Reported Pharmacokinetic Interactions of Dihydropyridines Following Consumption of GFJ in humans.



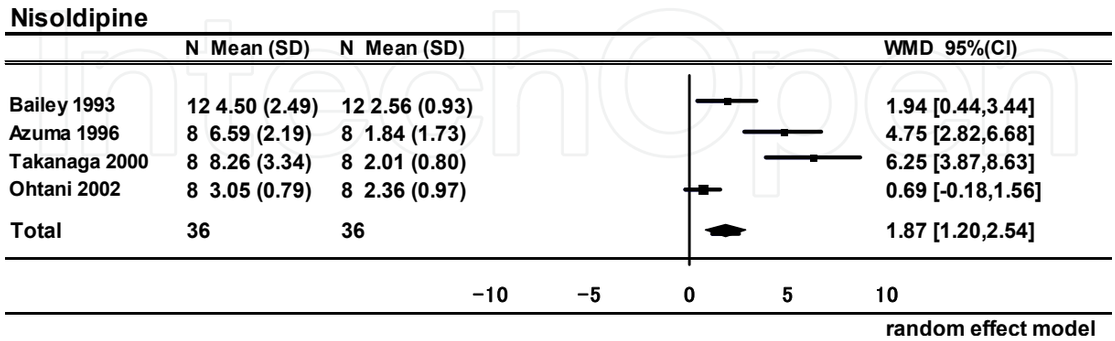
WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 7. Forest plot of the average difference of efonidipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.



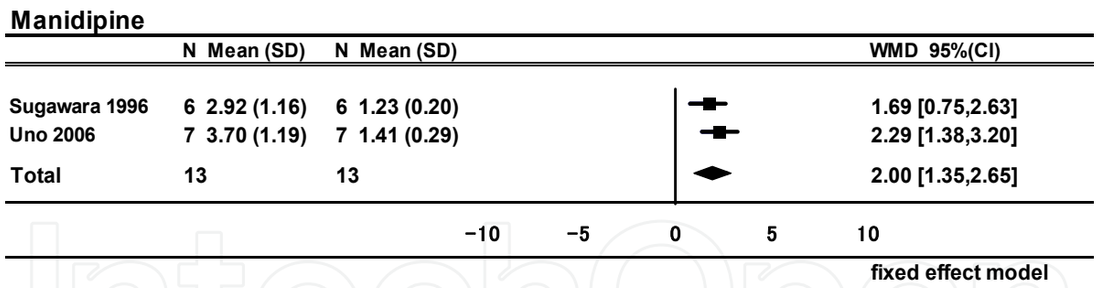
WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 8. Forest plot of the average difference of nifedipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.



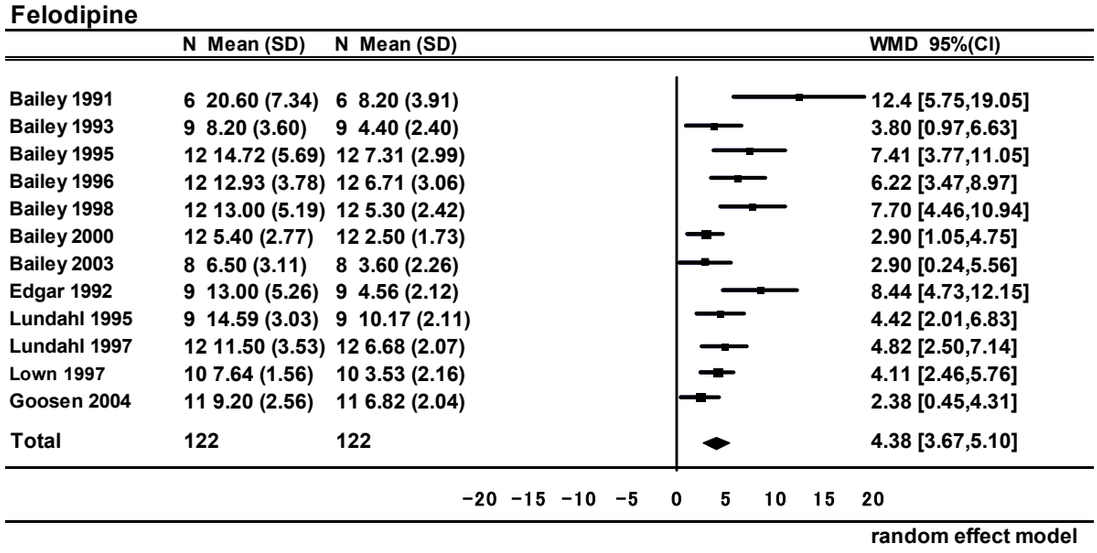
WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 9. Forest plot of the average difference of nisoldipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.



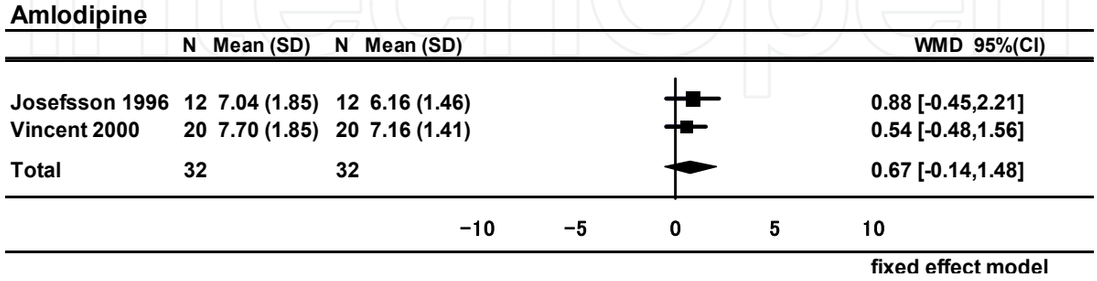
WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 10. Forest plot of the average difference of manidipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.



WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 11. Forest plot of the average difference of felodipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.



WMD and the 95% CI were calculated by the general variance-based method. This figure was cited from the literature (Uesawa et al., 2011b).

Fig. 12. Forest plot of the average difference of amlodipine AUC (nmol · h/L/mg dose) and the corresponding 95% CI from the studies included in the meta-analysis of GFJ-interactions.

2.5 Relationship between lipophilicities of 1,4-dihydropyridine derivatives and pharmacokinetic interaction strengths with GFJ

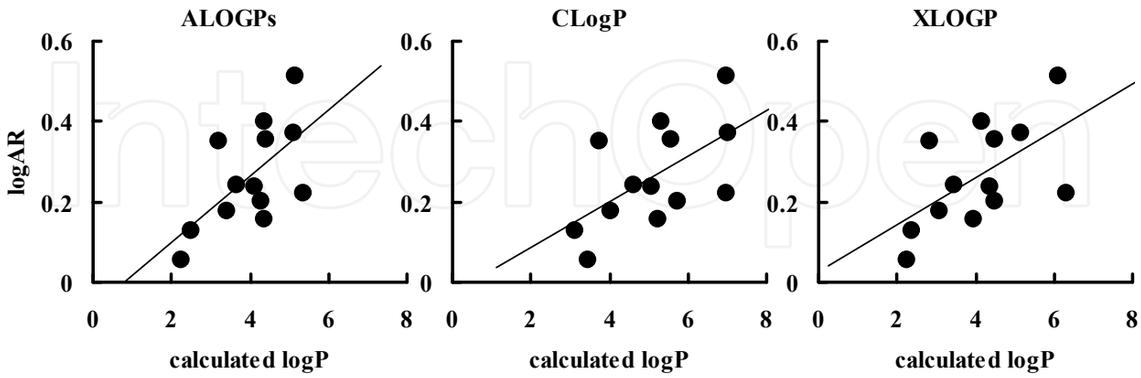
The structural and physicochemical properties of currently used 1,4-Dihydropyridine calcium channel antagonists vary significantly. However, little was known about the correlation between the structures and the clinical interaction strengths (CISs). Therefore analysis was performed using the predictive properties calculated from the chemical structures and the reported pharmacokinetic interactions with GFJ consumption (Uesawa & Mohri, 2008c). Thirteen dihydropyridines - amlodipine, azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and pranidipine - on which there were confirmable reports of pharmacokinetic interactions with GFJ, were selected for analysis. CISs were defined as common logarithmic values of the AUC increasing ratio, in which the AUC of each dihydropyridine with GFJ consumption was divided by the corresponding control AUC. The first report with a significant interaction with GFJ intake for each drug was referred to the AUC value to avoid the variation of CIS in publication bias. Three types of predicted logP values, ALOGPs (Tetko & Tanchuk, 2002), ClogP (Chou & Jurs, 1979), and XLOGP (Wang, 1997), and seven other physicochemical properties, water diffusion, molecular volume, molecular polarization, molecular density, refractive index, topologic polar surface area, and calculated molar refractivity, were calculated from the chemical structures. Analyses using the linear least-squares method for relationship between the physicochemical properties and CISs represent each logP value, CLogP, ALOGPs, and XLOGP, but not water diffusion, molecular volume, molecular polarization, molecular density, refractive index, topologic polar surface area, and calculated molar refractivity, correlated with CIS:

$$\text{CIS} = 0.0822\text{ALOGPs} - 0.0651,\ r = 0.626;\ \text{CIS} = 0.0569\text{ClogP} - 0.0276,\ r = 0.592;\ \text{CIS} = 0.0582\text{XLOGP} + 0.0272,\ r = 0.587 \text{ (Figure 13)}$$

Dihydropyridines have a 1,4-dihydropyridine ring as a common structure. This partial structure is characterized by substrates of cytochrome P-450, which form a pyridine ring as a result of the enzymatic reaction (Baarnhielm, 1984; Rush, 1986; Terashita, 1987). The aromatic-ring formation reaction is caused by the dihydropyridines losing their calcium antagonistic effect. Dihydropyridines used in clinical practice have a variety of chemical structures, suggesting various physicochemical and pharmacokinetic properties. In this study, findings from clinical trials were used in calculating CISs, and the conditions of pharmacokinetic investigation in the reports differed, resulting in errors among pharmacokinetic data. Nevertheless, the results showed that the relationship between CISs and the predicted logP values for the 13 dihydropyridines indicated significant correlation, which was expressed as simple linear regression formulae. These results suggest that the lipophilicity of the drugs is an important factor in the interactions.

It is considered that the clearance of dihydropyridines in first-pass metabolism is regulated by intestinal and hepatic intrinsic clearance. Because the target organ of GFJ is the intestine, it has been speculated that dihydropyridine with a higher contribution ratio of intestinal clearance in the first pass has stronger interaction with the concomitant consumption of GFJ. Ohnishi *et al*. reported that the plasma protein-binding ratio correlated with an increasing ratio of AUC for calcium-blocking agents with the consumption of GFJ (Ohnishi et al., 2006). This suggested the possibility that drugs that have higher plasma unbound fractions reflect

a higher percentage of contribution of the intestinal metabolism in first-pass effect due to a lower hepatic extraction ratio. LogP values are a parameter-informed correlation with the plasma protein binding of drugs (Kiehs, 1966; Yamazaki & Kanaoka, 2004) and, because of this, it is conceivable that the present results support the report showing a correlation between the extent of the interactions and protein-binding ratios. Furthermore, it is known that lipophilicity is one of the parameters contributing to absorption (Houston, 1975), distribution (Watanabe & Kozaki, 1978; Yamada, 1993), metabolism (Kim, 1991), and excretion (Cantelli-Forti, 1986; Yamada et al., 1993) in pharmacokinetics. For example, enzymatic affinities and kinetic properties in CYP oxidation of various compounds are regulated by the logP values of the substrates (Lewis, 2000). Therefore it is speculated that the lipophilicity of drugs contributes to the pharmacokinetic properties of dihydropyridines oxidizing with intestinal CYP3A. On the other hand, some dihydropyridines showed values that were distant from the linear regression in Figure 13. This observation possibly suggests that alternative factors other than CYP3A, such as drug transporters in the intestine, may be involved in the interactions. It has been reported that concomitant intake of GFJ causes an increase in the plasma concentration of P-glycoprotein substrates such as cyclosporine (Edwards, 1999) and a decrease in the plasma concentration of organic anion transporting peptide (OATP) substrates such as fexofenadine (Dresser, 2005). ALOGPs were considered to be the most appropriate algorithm to assess the interactions between the three types of predicted logP values examined in this study because they showed the best correlation. ALOGPs were used to predict the extent of GFJ interactions with dihydropyridines, which has not been reported to date. As a result, lercanidipine and niguldipine (ALOGPs: 6.42 and 6.27, respectively) were estimated to be high-risk drugs showing a predictive increase of 300% in the AUC with GFJ intake. Alternatively, it was suggested that aranidipine and nilvadipine (ALOGPs: 2.71 and 2.97, respectively) which are used in Japanese clinical practice, are relatively safe drugs comparable to nifedipine, which has a predicted AUC increase with GFJ of about 150%. The adequacy of these prognostics has yet to be demonstrated in terms of clinical trials, although the structural analyses in this study will be useful to predict the harmfulness of drugs in interactions with GFJ.



Lines are drawn with the least-squares approach.
AR: AUC ratio.
This figure was cited from the literature (Uesawa & Mohri, 2008c).

Fig. 13. Relationship Between Calculated LogP Values of Dihydropyridine Derivatives and the Corresponding Logarithmic AUC Ratios in Clinical Trials with GFJ Consumption.

2.6 Elimination of interacting components in GFJ

We found that BG and DHB in GFJ were unstable at high temperatures (Uesawa & Mohri, 2006). It is therefore proposed that the heat treatment of GFJ might serve as the basis for the removal of interactive FCs and thus the elimination of potential drug interactions. Furthermore, GFJ samples after heat treatment under various conditions, including various concentrations of FCs, are still useful for elucidating the functions of FCs in drug interactions. With such a background, we studied the effect of incubation at various temperatures on the concentrations of FCs in GFJ, and the actions of the GFJ samples on the drug interactions *in vitro* and *in vivo*. BG and DHB showed a consistent decrease during treatment at 95°C for 1 hr (Figure 14). Interestingly, the concentration of BT in GFJ was reversely increased in this condition. The increment of BT in GFJ rose to 14.1 μM after 60 min of treatment. At 4 and 37°C, each FC concentration did not almost change during incubation for 60 min (Figure 14). At 62, 72, and 95°C, concentrations of BG and DHB decreased in a temperature-dependent manner. The remainders of BG and DHB at 95°C for 60 min were 3.14 and 0.163 μM, respectively. On the other hand, the concentration of BT at 95°C for 60 min was 64.8 μM.

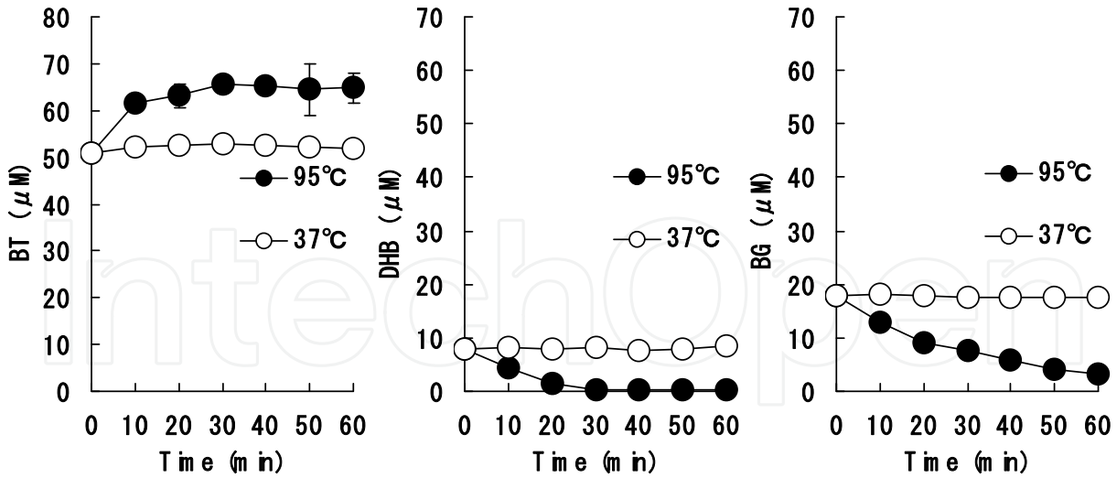
2.6.1 Inhibition of CYP3A activities

The testosterone 6β-hydroxylation rate was 2.14 nmol/min/mg protein in human liver microsomes; 10% of GFJ in the reaction mixture decreased the oxidation activity to 0.303 nmol/min/mg protein (14.1 % of the control, Figure 15). Treatment of GFJ at 95°C invalidated the inhibitory effect of GFJ by heat treatment in a time-dependent manner. The testosterone 6β-hydroxylation rate with GFJ heat-treated at 95°C for 60 min (HGJ) was 0.617 nmol/min/mg protein (28.8 % of the control). The remaining concentrations of BG and DHB, the important constituents in GFJ for drug interactions (section 1.3), in HGJ were 3.13 and 0.16 μM, respectively. On the other hand, BT, which does not contribute to CYP3A inhibition in GFJ, was increased to 64.8 μM in HGJ (Figure. 13). It was expected from these results that the CYP3A inhibitory effect and the pharmacokinetic interactions of GFJ would disappear as a result of heat treatment. Then, testosterone 6β-hydroxylation with human liver microsomes and GFJ treated at 95°C were measured in order to investigate the effect of the heating on CYP3A oxidation. As a result, the turnover rate of 6β-hydroxylation of testosterone decreased as the duration of heat treatment increased (Figure 15). The testosterone 6β-hydroxylation rates were negatively related to the concentrations of BG and DHB in GFJ samples treated at 95°C. These observations suggest that the lower amounts of BG and DHB in GFJ due to heating at 95°C controlled the inhibition of testosterone 6β-hydroxylation with GFJ. No study of inhibition of the CYP3A metabolism with FC-free GFJ has been reported. In this study, the remaining activities of CYP3A in the microsomal reactions with GFJ and HGJ were 14.1% and 28.8%, respectively, compared with the reaction without GFJ. It is believed that the 14.7% difference between the results with HGJ and GFJ stem from the net inhibition with BG and DHB in this condition. BG and DHB have structures constructed with BT, the simplest FC in citrus fruits, and isoprene side chains combined through the fifth oxygen atom of BT (Figure 2). It was reported that BG and DHB decrease oxidation for the drugs with mechanism-based inhibition of CYP3A expressed in small intestinal epithelial cells (Ameer & Weintraub, 1997). On the other hand, BT did not inhibit CYP3A activities in microsomes from humans and rats (Mohri & Uesawa, 2001a; Row, 2006).

2.6.2 Effects of HGJ on nifedipine pharmacokinetics

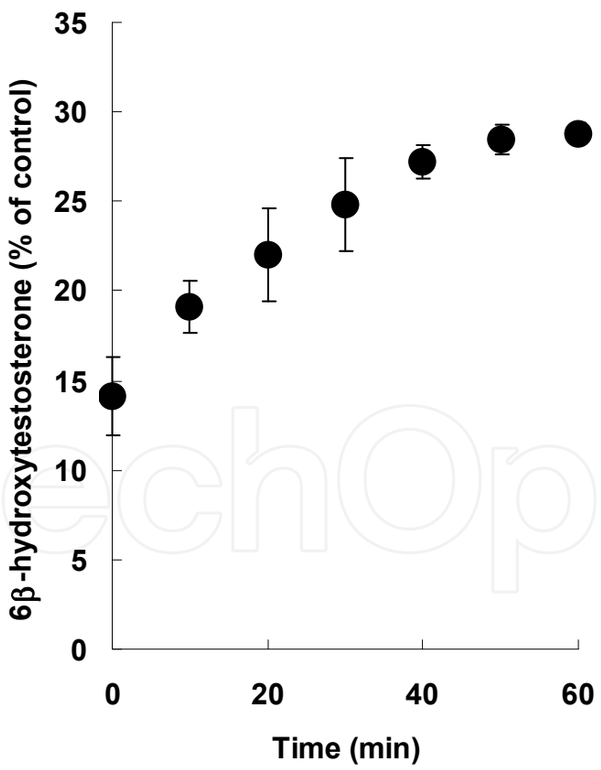
It was shown that HGJ produced a CYP3A-inhibitory effect of 71% in comparison with untreated GFJ. Therefore the effects of HGJ on nifedipine pharmacokinetics in rats were evaluated in vivo. We have shown, in earlier studies, that the AUC of nifedipine is significantly increased by the intraduodenal administration of GFJ but not of orange juice, sweetie juice, or saline (Mohri, 2000; Mohri & Uesawa, 2001a; Uesawa & Mohri, 2005). These results suggest that GFJ caused increased gastrointestinal absorption of nifedipine in rats. It was thought that nifedipine oxidation by CYP3A in the intestinal mucosa was inhibited by GFJ administration. Actually, our rat studies with small intestinal microsomes (Mohri & Uesawa, 2001b) indicated that BG and DHB contribute to the inhibition of nifedipine oxidation in rat small intestine (Mohri & Uesawa, 2001a). These observations in rats are very similar to those in humans (Lown et al., 1997). These observations suggest that evaluation using rats is useful for predicting drug-food interactions. Therefore the effect of HGJ administration on nifedipine pharmacokinetics using rats was investigated in this study. Injection of HGJ into the duodenum 30 min before nifedipine administration did not affect the plasma concentration/time profile of nifedipine (Figure 16). On the other hand, the AUC and C_{max} were significantly increased in the GFJ-preadministered group compared with the HGJ-administered group. These observations show that the administration of HGJ, unlike that of GFJ, probably does not increase the small intestinal absorption of nifedipine. The results also suggest that inhibitory contents of CYP3A in HGJ, as observed in the in vitro experiments, because of the disappearance of BG and DHB in HGJ, do not contribute pharmacokinetic interactions between nifedipine and GFJ. Mechanism-based inhibitors such as BG and DHB may be able to reduce the activity of CYP3A in the intestinal tract effectively (Ameer & Weintraub, 1997). In fact, unlike GFJ, naringin, a potent, but not mechanism-based inhibitor of CYP3A (Guengerich & Kim, 1990), has been reported not to increase the availability of nisoldipine in humans (Bailey et al., 1993b).

These investigations clearly showed the contributions of FCs on drug interactions with GFJ in *in vitro* and *in vivo* experiments using GFJ samples, eliminated BG and DHB following high temperature treatments. Furthermore, these observations may develop as fundamental knowledge to create "drinkable GFJ" for patients receiving medications that induce interactions with GFJ. In the previous report, we showed that sweetie juice did not have a significant effect on nifedipine pharmacokinetics in rats (Uesawa & Mohri, 2005). The concentrations of BG and DHB in the sweetie juice used in the study were 1.6 and 0.51 μM, respectively. In other words, low FC concentrations such as that in sweetie juice and HGJ hardly relate to drug bioavailability. Examination of the respective threshold concentrations of the FCs is important in terms of pharmacokinetics in order to ensure the quality of the GFJ from which FCs have been removed. On the other hand, heat treatment at 95 °C in the present basic study seems to have a detrimental effect on the taste, flavor and nutrients of GFJ. However, it might be possible to develop GFJ processing methods with lower temperatures thereby avoiding these problems, as, the concentrations of BG and DHB in GFJ are low at 62 °C. In addition, understanding the thermal decomposition mechanism of FCs may enable the selection of effective low-temperature catalysts. Although it is necessary to examine the heating condition, we presumed that the results of the heat treatment of GFJ will contribute to the development of practical research on the prevention of drug interactions, and may contribute to resolving this problem in clinical settings. This study offers a new method that is applicable in research on drug interaction with various food and drinks.



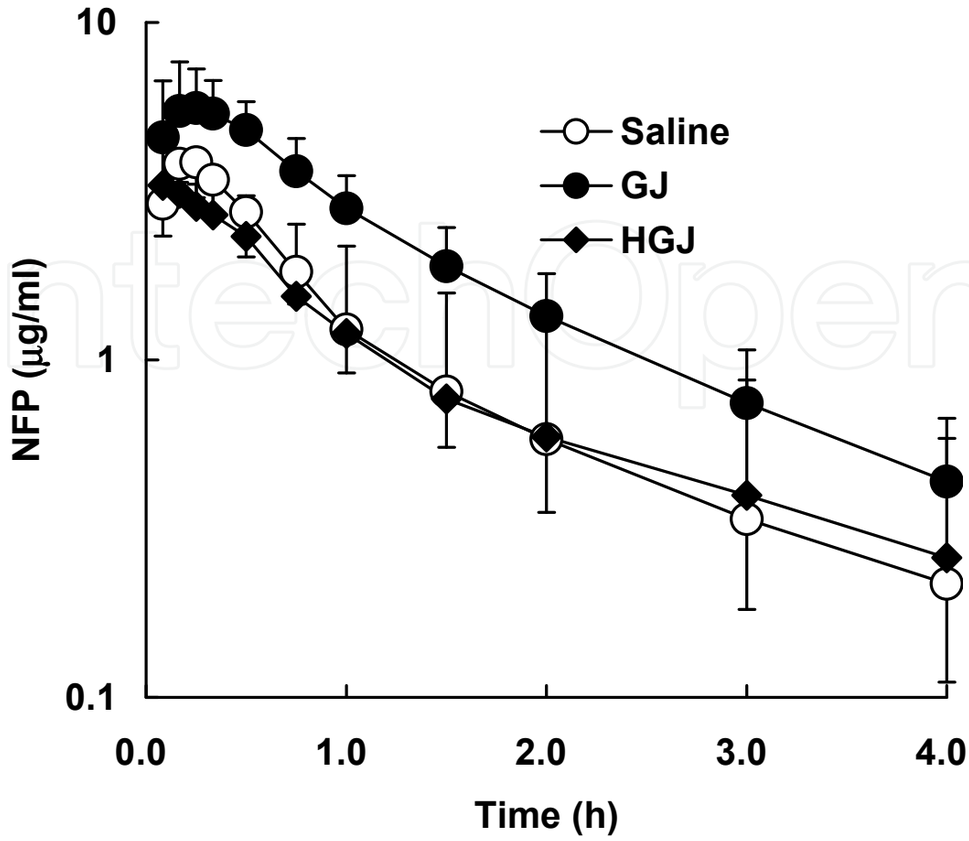
The concentrations were determined in duplicate as described under Materials and Methods. Each point and vertical bar represents the mean and range. This figure was cited from the literature (Uesawa & Mohri, 2006).

Fig. 14. BT, DHB, and BG concentrations in the GFJ treated at 37°C and 95°C for 0, 10, 20, 30, 40, 50, and 60min.



The control mixture included no GFJ. Each point and vertical bar represents the mean and S.D. (n=3). This figure was cited from the literature (Uesawa & Mohri, 2006).

Fig. 15. 6β-oxidation rates of testosterone with human liver microsomes and the GFJ treated at 95°C for 0, 10, 20, 30, 40, 50, and 60 min.



Dose of nifedipine=3mg/kg. Five rats were used in each group. Each point and vertical bar represents the mean and S.D. (n=5). This figure was cited from the literature (Uesawa & Mohri, 2006).

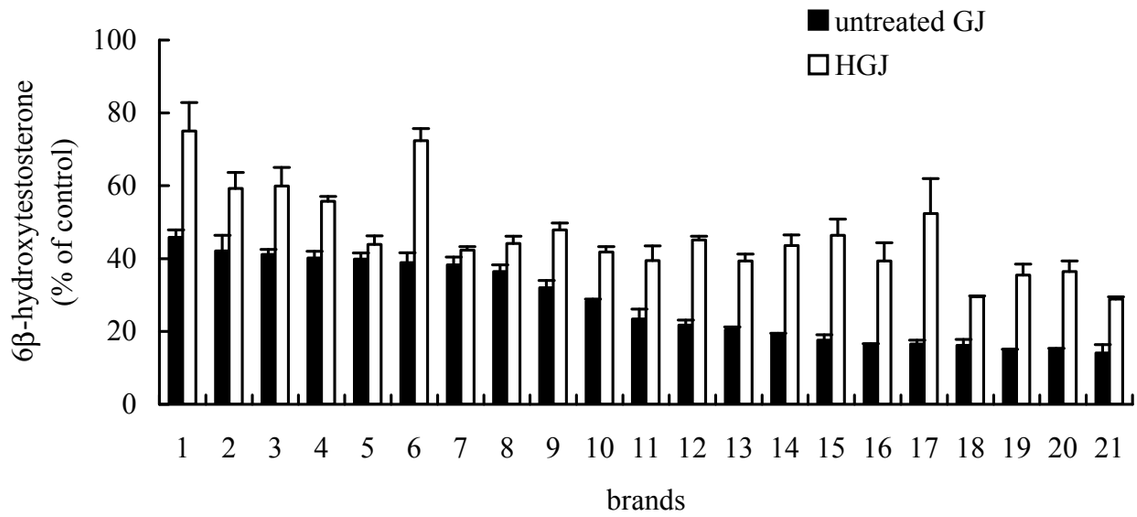
Fig. 16. Plasma concentration-time curves for nifedipine after i.d. administration of nifedipine 30 min after administration of 2 mL of saline, GFJ, and HGJ to the duodenum.

2.7 Variation of concentrations of furanocoumarin derivatives in GFJ brands

2.7.1 Drug-interaction potentials among different brands of GFJ

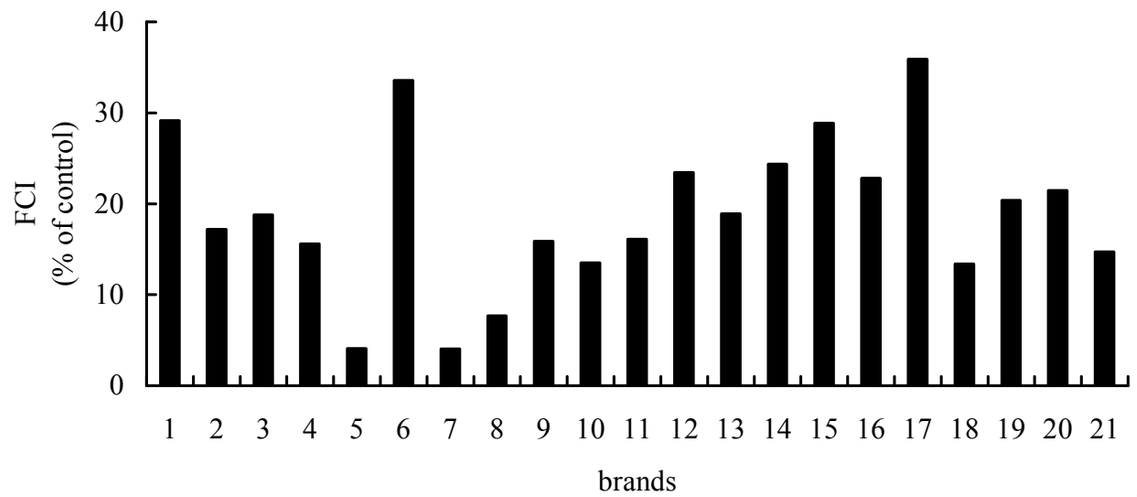
We discovered that heat treatment of GFJ decreased concentrations of furanocoumarin derivatives, bergamottin and 6',7'-dihydroxybergamottin, depending on the temperature and the treatment period, thereby causing the inhibitory effect on CYP3A to decrease and the pharmacokinetic interaction potential to disappear (Section 1-6). These findings suggest that heat treatment of GFJ may be applicable in the evaluation of GFJ-drug interactions from furanocoumarins, suggesting that the decrease in the CYP3A inhibitory potential of GFJ by the heat treatment was related to the concentrations of furanocoumarins present in GFJ. In this section, variations in the drug-interactions among 21 different brands of GFJ were estimated using heat treatment to analyze the potentials of furanocoumarin-caused CYP3A-inhibitions (Uesawa & Mohri, 2008b). Heat treatment of the GFJ at 95 °C for 1h was utilized to degrade the furanocoumarins. Initial velocity of testosterone 6β-oxidation using human liver microsomes was determined as an indicator of the CYP3A activities. The initial rates of CYP3A dependent testosterone 6β-oxidation in human liver microsomes were measured with various brands of GFJ and heat-treated GFJ (HGJ). As a result, when compared with

the corresponding brand of untreated GFJ, all brands of HGJs indicated significantly lower efficacy in the inhibition of the CYP3A oxidation, except for one brand that showed no significant change (Figure 17). The inhibitory effects of untreated GFJ and HGJ ranged from 54.2 to 85.9 % and from 25.0 to 71.1%, respectively. The differences between the two, caused by the loss of furanocoumarins in heating, were defined as net potentials of furanocoumarin-induced CYP3A inhibitions (FCIs) and expressed as percentages compared with the control velocity in a 6β - hydroxytestosterone - production reaction without GFJ (Figure 18). The results show that FCIs ranged from 4.0 to 35.9%.



The control mixture included no GFJ. Each point and vertical bar represents the mean and S.D. (n=3). This figure was cited from the literature (Uesawa & Mohri, 2008b).

Fig. 17. 6β-oxidation rates of testosterone with human liver microsomes and untreated GFJ or HGJ.



This figure was cited from the literature (Uesawa & Mohri, 2008b).

Fig. 18. FCI values in each GFJ sample.

The component inhibitory potentials eliminated by the heat treatment of GFJ may be able to reflect the action *in vivo*. The results indicate that heat treatment could be useful in evaluating the potencies of GFJs in the drug interactions caused by furanocoumarins. It is believed that the *in vitro* evaluation systems using only untreated GFJ do not properly reflect the GFJ - drug interactions *in vivo* because these interactions are induced by furanocoumarin derivatives such as bergamottin and 6',7 '- dihydroxybergamottin in GFJ. Figure 17 and 18 show that order of each bland on the interaction potential estimated by FCI is not necessarily corresponding to the case estimated by only untreated GFJ. Therefore, we suggest that the inhibition potential of GFJ may be estimated by subtracting the microsomal CYP3A activity with HGJ from those activities obtained with the corresponding untreated GFJ. It is anticipated that the technical measurements of the GFJ-drug interaction potentials using FCI established in the present study, may be an effective method to identify the intensity of GFJ in the interactions.

3. Citrus juice interactions related with the decrease of plasma drug concentrations

Recently, citrus juices such as GFJ and orange juice can prevent the intestinal absorption of some β-blockers. As a result of this type of interactions, plasma concentrations of drugs are decreased. In this section, this type of interaction will be described.

3.1 Antihypertensive drugs related with the citrus juice interactions

In addition to increasing drug absorption with GFJ, citrus juices such as GFJ and orange juice can also prevent the intestinal absorption of drugs. For example, the intestinal absorption of fexofenadine, a third-generation antihistamine, is inhibited by GFJ, orange juice, and apple juice (Dresser, 2002). Furthermore, GFJ and orange juice also inhibit absorption of the ß-blocking agents, celiprolol (Lilja, 2003, 2004), atenolol (Lilja, 2005b), acebutolol (Lilja, 2005a), and talinolol (Schwarz, 2005).

3.2 Mechanism of the citrus juice interactions

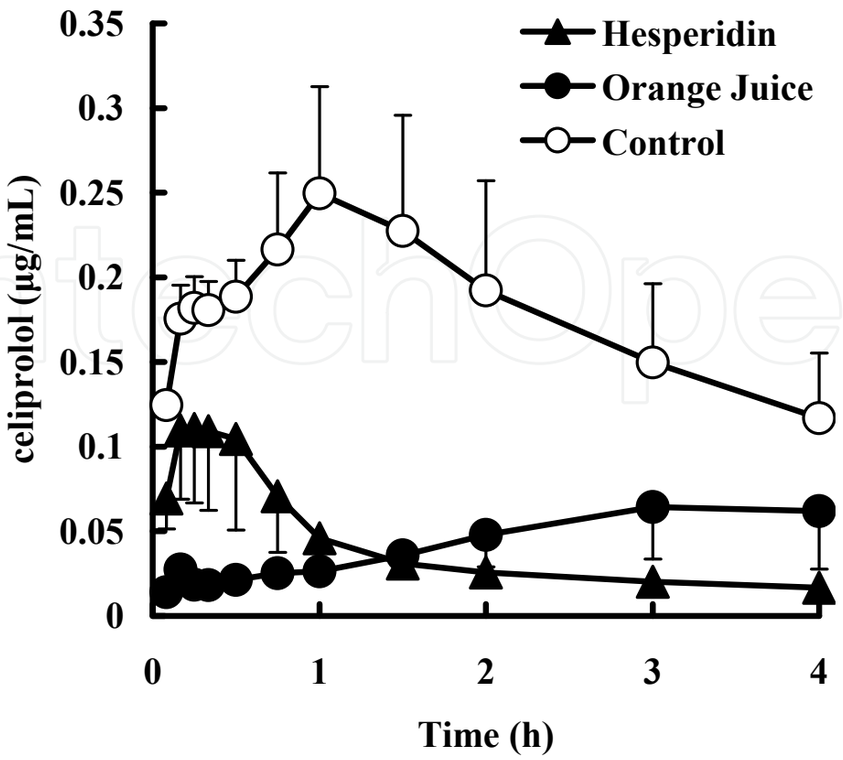
It was reported that the citrus juice interactions are caused by inhibition of drug-transporting ability of intestinal organic anion transporting polypeptide (OATP) with contents in citrus juices. Fexofenadine is taken up by intestinal epithelial cells via OATP, which is expressed on the apical membrane, in the first step of absorption into general circulation from intestinal lumen (Dresser et al., 2002, 2005; Nozawa, 2004). Interestingly, GFJ enhances the intestinal absorption of talinolol in rats, putatively through inhibiting MDR1 activity and decreasing efflux from epithelial cells (Spahn-Langguth & Langguth, 2001). In humans, however, GFJ inhibits the intestinal absorption of talinolol (Schwarz et al., 2005). These observations suggest that in GFJ interactions with substrates of both of MDR1 and OATP, OATP uptake may dominate MDR1 efflux in humans but not in rodents.

3.3 Citrus juice components involved in drug interactions

Naringin, the major ingredient in GFJ, blocks the uptake of fexofenadine by the intestinal cells (Bailey, 2007). Hesperidin, a major component of orange juice, also inhibits intestinal absorption of celiprolol (Uesawa & Mohri, 2008a). Hesperidin is a flavonoid glycoside with

a similar molecular structure to naringin. Hesperidin and naringin both inhibit the transport of OATP1A2 (Bailey et al., 2007), which mediates the intestinal uptake and systemic accessibility of ß-blockers, providing a mechanism for inhibiting absorption (Bailey et al., 2007).

In this section, our findings related with demonstration of a causal ingredient of the pharmacokinetic interaction between orange juice and celiprolol. It has been reported that the bioavailability of celiprolol is decreased by interaction with orange juice as well as GFJ because of inhibition of intestinal absorption of the drug (Lilja et al., 2004). We attempted to characterize this interaction by means of pharmacokinetic experiments with rats. Figure 19 shows pharmacokinetic profiles of plasma celiprolol levels when celiprolol with water (control), orange juice, and hesperidin solution were injected into the rat duodenum. However, under the abundant period of the elimination phase, especially for the orange juice group, the pharmacokinetic parameters were calculated in the period for descriptive purposes as well as other groups. AUC of celiprolol in the orange juice group was significantly decreased by 75.3 % compared with the control group. This observation corresponds with results in humans in which the AUC of celiprolol decreased by 83 %. It has been known in detail that when fexofenadine is taken with grapefruit or orange juice, both plasma concentration and AUC are decreased, as in the case of celiprolol. It has been reported that naringin, a major ingredient in GFJ, was the cause of the pharmacokinetic interaction between GFJ and fexofenadine (Bailey et al., 2007). Hesperidin, a major component of orange juice, is a flavonoid glycoside with an appearance and molecular structure similar to that of naringin. It has been demonstrated that hesperidin as well as naringin inhibit the transport of OATP1A2, an intestinal transporter related to the absorption of fexofenadine (Bailey et al., 2007). OATP1A2 probably facilitates the intestinal uptake and systemic accessibility of a broad battery of orally administered medications (Lee, 2005; Glaeser, 2007). Rat intestinal oatp3 is an orthologue of human OATP1A2 (Dresser et al., 2002). Although the mechanism of inhibition of celiprolol absorption by orange juice is unknown, flavonoids possibly contribute to the interaction because celiprolol undergoes inhibition with both orange juice and GFJ in the same way as fexofenadine. In fact, hesperidin as well as naringin affected significantly the uptake of fexofenadine by rat oatp3 (Dresser et al., 2002). We therefore designed our study with rats with the intention of identifying the role of hesperidin in orange juice in the interaction with celiprolol. As a result of the administration of celiprolol with hesperidin, significant decreases in AUC were observed compared with control, as also in the case of concomitant orange juice administration. On the other hand, the AUC in the hesperidin group was not significantly different from that in the orange juice group. These results demonstrate that hesperidin in orange juice contributes to the interaction observed. Inhibition of the celiprolol transporting pathway by hesperidin in the intestine is a possible mechanisms as is the case with fexofenadine - orange juice interaction. Furthermore, physicochemical effects such as binding and degradation of celiprolol with hesperidin might also contribute to the reduction in plasma concentrations due to decreased solubility and absolute amount of the drug in the intestinal duct. Initial decrementation of the celiprolol concentration in plasma by the coadministration of orange juice was greater than that due to hesperidin (Figure 19). In the rats receiving orange juice but not hesperidin, Tmax was also elongated significantly compared with controls. These observations suggest that a component or components of orange juice other than hesperidin may also contribute to variations in the absorption kinetics of celiprolol.



Dose of celiprolol was 5 mg/kg body weight. Each point and vertical bar represents the mean and S.E., respectively (n=4 - 5). This figure was cited from the literature (Uesawa & Mohri, 2008a).

Fig. 19. Plasma concentration-time curves for celiprolol after it was administered into the duodenum of rats with water (control, white circle), orange juice (black circle) and 207.7 μg/mL hesperidin aqueous solution (black triangle).

4. Conclusion

Accumulated knowledge of pharmacokinetic interactions of antihypertensive drugs with citrus juices was mentioned in this chapter. Furthermore, characteristics and mechanisms of the interactions were described with the latest results in the research studies. Drug-citrus juice interactions are a complicated phenomenon, with increasing and decreasing drug concentrations in plasma which is dependent on the combinations of drugs and juices. However, I believe that applicable instruction based on an understanding of the mechanisms for patients undergoing pharmaceutical therapies, will be useful. This will enable them to avoid such interactions.

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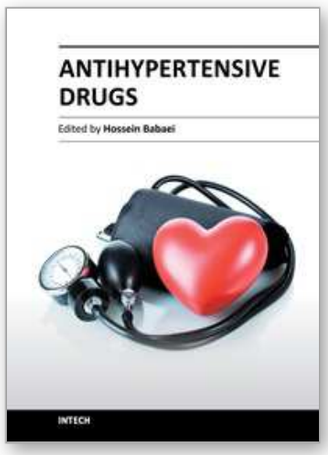

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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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