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Effects of cranberry juice on nifedipine pharmacokinetics in rats

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Abstract

Little information is available about drug interactions with cranberry juice (CJ). Using microsomes from the human liver and rat small intestine, this study was designed to determine whether CJ could inhibit CYP3A-mediated nifedipine (NFP) oxidase activity; it showed that CJ was a potent inhibitor of human and rat CYP3A. Preincubation with 10% vol/vol of CJ and 1 mM NADPH for 10 min resulted in significant inhibition of the NFP oxidation activity of human and rat CYP3A (18.2 and 12.6% decreases, respectively, compared with preincubation experiments without NADPH). In addition, the pharmacokinetic interaction between CJ and NFP in vivo was confirmed in rats. In comparison with a control group, the area under the concentration–time curve (AUC) of NFP was approximately 1.6-fold higher when CJ (2 mL) was injected intraduodenally 30 min before the intraduodenal administration of NFP (30 mg kg^{-1}). However, the mean residence time, the volume of distribution and the elimination rate constant were not changed significantly. These data suggest that CJ component(s) inhibit the function of enteric CYP3A. In conclusion, it was found that CJ inhibits the CYP3A-mediated metabolism of NFP in both rats and humans. Furthermore, CJ alters NFP pharmacokinetics in rats.

Introduction

Cranberry (*Vaccinium macrocarpon*) belongs to the family Ericaceae. This fruit and its products have been associated historically with many positive effects on human health, and cranberry juice (CJ) has become popular as a health food supplement. Based on some evidence, including epidemiologic studies, it is believed that CJ is effective in the prevention of urinary tract infections (Avorn et al 1994; Foxman et al 1995). Furthermore, it has been reported that CJ may be effective in inhibiting *Helicobacter pylori* adhesion (Burger et al 2000; Zhang et al 2005) and preventing influenza (Weiss et al 2005). At the same time, there are case reports showing the possibility of side-effects due to the consumption of CJ, particularly involving the anticoagulant drug warfarin (Suvarna et al 2003; Grant 2004). Specifically, one patient drinking CJ and also taking warfarin died of a gastrointestinal and pericardial haemorrhage. The Committee on the Safety of Medicines in the UK has advised that it is sensible for patients taking warfarin to limit their intake of this drink. The effects and drug interactions with CJ might be related to the fact that the juice is rich in flavonol glycosides, anthocyanins, proanthocyanidins, and organic and phenolic acids (Seeram et al 2004). It is believed that these chemicals in CJ will be shown to have pharmacokinetic interactions with drugs owing to their inhibition of the cytochrome P450 mixed-function monooxygenase system because the plasma concentrations and effectiveness of warfarin are controlled by metabolism with CYP2C9 and CYP3A4 in human liver. However, no information about the effects of CJ consumption on drugs has been reported except in the case of warfarin. As a typical example of the interaction between drugs and foods, increases in the blood concentration of some kinds of drugs such as antihypertensive dihydropyridine derivatives, including nifedipine (NFP), due to the ingestion of grapefruit juice (GJ) have been reported (Bailey et al 1989; Sagir et al 2003). It is known that interactions between GJ and drugs depend on the inhibition of CYP3A4 in the gastrointestinal tract containing franocoumarin derivatives. It has also been reported that Seville orange juice (Di Marco et al 2002), pomegranate juice (Hidaka et al 2005) and pomelo juice (Egashira et al 2003)

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cause interactions similar to those of GJ. Drug interactions with CJ were therefore investigated in the present study.

Materials and Methods

Chemicals

NFP and NFP oxide (NFPO) were kindly donated by Kanebo Pharmaceuticals Ltd (Osaka, Japan). Nitrendipine (NTP) (internal standard, IS) was obtained from Yoshitomi Pharmaceutical Industries Ltd (Osaka, Japan). NFP and NTP were always handled under subdued light. Anthracene (internal standard 2, IS2) was obtained from Wako Pure Chemical Industries Ltd (Osaka, Japan). Bergamottin and 6′,7′-dihydroxybergamottin were purchased from Daiichi Pure Chemicals Co. Ltd (Tokyo, Japan). Bergaptol was obtained from Funakoshi Co. Ltd (Tokyo, Japan). Rat small intestinal microsomes were prepared according to a previously described method involving EDTA separation of enterocytes and ultracentrifugation (Mohri & Uesawa 2001a). Pooled human hepatic microsomes were obtained from BD Biosciences (San Jose, CA, USA). Methanol, acetonitrile and phosphoric acid of HPLC grade were used (Wako). All other chemicals were reagent grade (Wako). Water was used after double-distillation in a glass still. CJ and GJ were obtained from Kodama Natural Foods Co. Ltd (Fukuoka, Japan) and Kanda Foods Laboratory Co. Ltd (Tokyo, Japan), respectively.

Animals and drug administration

NFP was administered to rats according to a previously described method (Mohri & Uesawa 2001b). Briefly, male Wistar–ST rats (Nihon SLC Co., Shizuoka, Japan), weighing 280–300 g, were used throughout the study. The femoral vein was cannulated with PE-10 tubing (Clay Adams, Parsippany, NJ, USA) for saline infusion. The femoral artery was cannulated with PE-50 tubing (Clay Adams) to collect blood samples at 0, 5, 10, 15, 20, 30 and 45 min, and 1.0, 1.5, 2.0, 3.0 and 4.0 h after NFP administration, with an established heparin lock using 100 units mL^{-1} heparin in saline. Two millilitres of fruit juices or saline were directly injected into the duodenum. After 30 min, NFP was administered at a dose of 3 mg kg^{-1} body weight into the duodenum. The blood samples collected were immediately centrifuged at 16 000 *g* for 15 min at 4°C; the plasma was then separated. At this point 180 μL of IS solution (1 μg mL^{-1} NTP in acetonitrile) was added to 20 μL of the plasma in a 2-mL plastic tube. After being shaken vigorously, the sample was centrifuged at 16 000 *g* and 4°C for 10 min; 25 μL of the supernatant was injected directly into the HPLC system as previously described (Mohri & Uesawa 2001b). Briefly, the HPLC system was equipped with a UV/VIS detector (UV-1570, JASCO Corp. Ltd, Tokyo, Japan) and a reversed-phase analytical Capcell Pak UG-ODS column (4.6 mm inside diameter × 25 cm; particle size 5 μm; Shiseido Co. Ltd (Tokyo, Japan)). A mobile phase consisting of 0.085% of phosphoric acid/acetonitrile (55:45, vol/vol) was pumped through the column at a speed of 1.0 mL min^{-1}. NFP was quantified at a wavelength of 260 nm. Calibration curves (0.63 to 20 μg mL^{-1} of NFP) were drawn by linear least-squares regression analysis. The detection limit for NFP was 0.05 μg mL^{-1}. The plasma concentration–time data (0 to 4 h) from each animal were analysed using a model-independent method with the MULTI computer program (Yamaoka & Nakagawa 1983). All animal procedures were approved by the Meiji Pharmaceutical University Committee for Ethics of Experimentation and Animal Care.

Assay of NFP oxidation activities of microsomes

An assay of the NFP oxidation activity with microsomes from rat intestine and human liver was performed according to a previously described method (Mohri & Uesawa 2001b), with minor modifications. Briefly, the microsomes (150 μg) were preincubated in 10% CJ or GJ in 0.1 M sodium phosphate buffer (pH 7.4) with or without NADPH (1 mM) (final incubation volume, 30 μL) for 10 min. An aliquot (10 μL) of the reaction mixture was transferred to a 2-mL plastic tube containing NFP (500 μM) and NADPH (1 mM) in 0.1 M sodium phosphate buffer (pH 7.4) (final volume 120 μL). After 10 min of incubation, acetonitrile (200 μL) and saturated aqueous ammonium sulfate (120 μL) were added to the reaction mixture. The sample was mixed vigorously for 20 s and centrifuged at 16 000 *g* for 5 min at 4 °C, then the organic layer (25 μL) was injected into the HPLC system as previously described to analyse the NFPO produced from NFP by the enzymatic reaction. Briefly, the HPLC system was as described in the previous section with a mobile phase consisting of 0.085% of phosphoric acid/acetonitrile/methanol (55:20:30, vol/vol/vol). NFPO was quantified at a wavelength of 280 nm. Calibration curves (0.5 to 10 μM of NFPO) were drawn by linear least-squares regression analysis. The detection limit for NFPO was 0.05 μg mL^{-1}. The control was incubated with water instead of fruit juice.

Detection of furanocoumarin derivatives in CJ and GJ

The detection of furanocoumarin derivatives in CJ and GJ was performed according to a previously described method (Mohri & Uesawa 2001b). Briefly, the juice samples were analysed using HPLC equipped with a reverse-phase analytical Capcell Pak SG-Phenyl column (4.6 mm inside diameter × 25 cm; particle size 5 μm; Shiseido Co. Ltd (Tokyo, Japan)). A photodiode array detector (MD-910, JASCO Corp. Ltd, (Tokyo, Japan)) was used because it reveals the characteristic UV-absorption spectrum of furanocoumarin derivatives, commonly with 311 nm as the maximum wavelength (Uesawa & Mohri 2005a). A mobile phase consisting of 0.1% phosphoric acid and acetonitrile was pumped through the column at a speed of 1.0 mL min^{-1} with a gradient of 0 to 5 min, 40% acetonitrile, and subsequently from 40 to 100% acetonitrile in 30 min. Then 400 μL of IS2 solution (10 μg mL^{-1} anthracene in acetonitrile) was added to 100 μL of the CJ in a 2-mL plastic tube. After being shaken vigorously, the sample was centrifuged at 16 000 *g* and 4°C for 10 min; 50 μL of the supernatant was injected directly into the HPLC system. Calibration curves (1 to 50 μg mL^{-1} of

bergamottin, 6′,7′-dihydroxybergamottin and bergaptol) were drawn by linear least-squares regression analysis. The detection limits for bergamottin, 6′,7′-dihydroxybergamottin and bergaptol were 0.1, 0.1 and 0.05 $\mu g\,mL^{-1}$, respectively.

Data analysis

All data are expressed as mean ± s.d. An unpaired Student's *t*-test and one-way ANOVA, followed by least-significant-difference analysis, were used to test for significant differences in mean values. The significance level was set at $P < 0.05$. AUC was calculated from the values obtained using the trapezoidal rule (0 to 4 h).

Results

NFP oxidation activity in rat small intestinal microsomes and human liver microsomes

Figure 1A shows the effects of fruit juice on the NFP oxidation activity in human liver microsomes. In the control investigations, no significant difference in NFP oxidation activity was observed between microsomes pre-incubated with or without NADPH (1.63 ± 0.10 and $1.61 \pm 0.04\,nmol\,min^{-1}\,mg\ protein^{-1}$, respectively). The NFP oxidation activity in the investigation with NADPH was significantly decreased by the addition of CJ and GJ compared with the case without NADPH, as shown by * (decreases of 18.2 and 62.7%, respectively). The activity was only slightly but significantly decreased by CJ but not affected by GJ in the absence of NADPH during preincubation, as shown by † (decrease of 6.0%). Figure 1B shows the effects of fruit juice on NFP oxidation activity in rat small intestinal microsomes. In the control investigations using water instead of fruit juice, no significant difference in NFP oxidation activity was observed between microsomes with or without NADPH during preincubation (0.485 ± 0.047 and $0.474 \pm 0.057\,nmol\,min^{-1}\,mg\ protein^{-1}$, respectively). However, the NFP oxidation activity in the investigation with NADPH during preincubation was significantly decreased by the addition of CJ and GJ compared with the case without NADPH, as shown by * (decreases of 12.6 and 58.8%, respectively). The activity

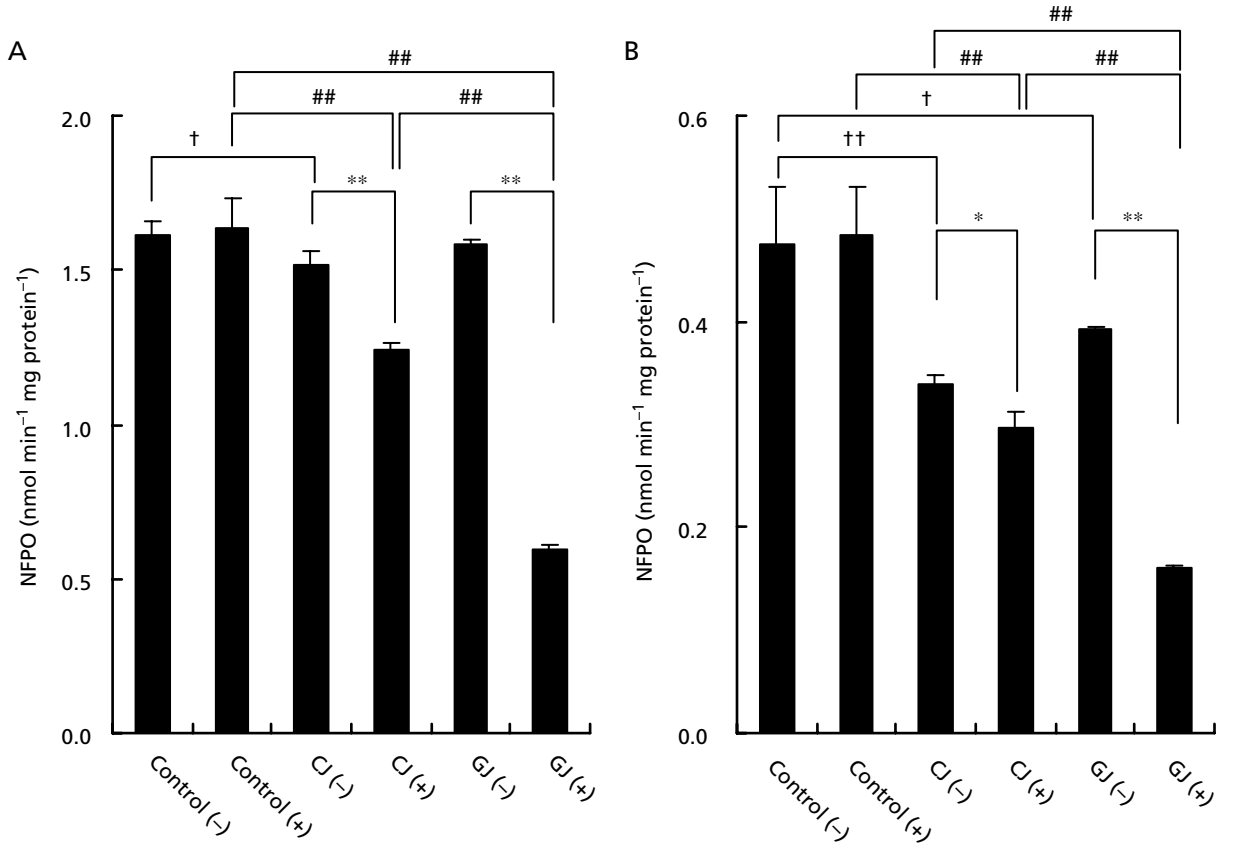

Figure 1 Effects of CJ and GJ on the NFP oxidation activity in microsomes from human liver (A) and rat small intestine (B). (+) and (−) represent the investigations with or without NADPH during preincubation, respectively. The activities were determined in triplicate as described in the Materials and Methods section. Each point and vertical bar represent the mean and s.d. (n = 3). *$P < 0.05$ and **$P < 0.01$, the results of CJ, GJ and control with NADPH were compared with the values under the same conditions without NADPH during preincubation. †$P < 0.05$ and ††$P < 0.01$, comparison between the values for CJ, GJ and control without NADPH during preincubation. ##$P < 0.01$, comparison between the values for CJ, GJ and control with NADPH during preincubation.

was decreased significantly by CJ and GJ in the absence of NADPH during preincubation, as shown by † (decreases of 28.6 and 17.4%, respectively).

Effects of CJ on NFP pharmacokinetics in rats

The NFP plasma concentration–time profiles after CJ, GJ and saline administration to rats are shown in Figure 2. After intraduodenal (i.d.) administration, the mean AUC values of the rats receiving CJ and GJ were approximately 1.64 and 1.61 times and the mean apparent clearance (CL/F) values were approximately 0.61 and 0.56 times greater, respectively, than those of the rats receiving saline (Figure 2, Table 1). On the other hand, the mean residence time (MRT), apparent volume of distribution (V_{dss}), elimination rate constant (K_{el}), maximal concentration in plasma (C_{max}), and time reached to C_{max} (T_{max}) were not significantly different between saline administration and CJ or GJ.

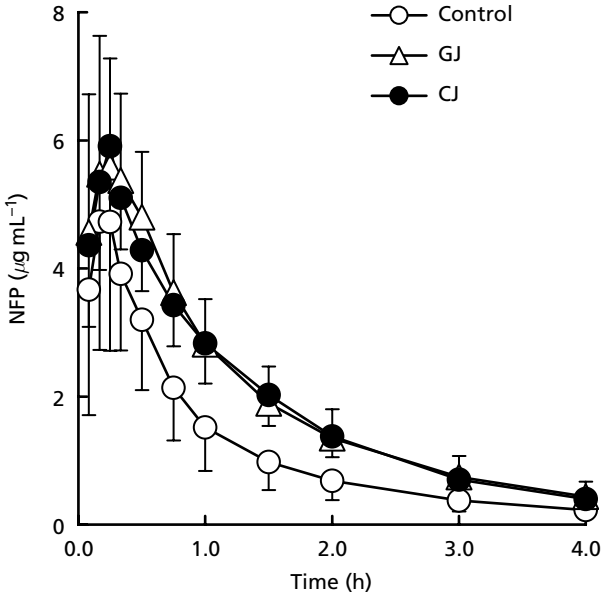

Figure 2 Plasma concentration–time curves for NFP after i.d. administration of NFP 30 min after administration of 2 mL of CJ (●), GJ (△) or saline (○) to the duodenum. Dose of NFP = 3 mg kg^{-1}. Five rats were used in each group. Each point and vertical bar represent the mean and s.d.

Table 1 Pharmacokinetic parameters of NFP in rats pre-administered saline, GJ or CJ

Parameter	Saline	GJ	CJ
AUC (μg h mL^{-1})	5.29 ± 1.78	8.65 ± 2.73*	8.52 ± 1.22*
MRT (h)	1.47 ± 0.40	1.56 ± 0.33	1.64 ± 0.67
CL/F (L/h)	0.18 ± 0.05	0.11 ± 0.03*	0.10 ± 0.01*
V_{dss} (L)	0.27 ± 0.11	0.17 ± 0.04	0.16 ± 0.06
K_{el} (h^{-1})	0.55 ± 0.14	0.60 ± 0.11	0.72 ± 0.34
T_{max} (h)	0.20 ± 0.05	0.27 ± 0.14	0.25 ± 0.06
C_{max} (μg mL^{-1})	5.02 ± 1.90	5.98 ± 1.73	6.11 ± 1.27

GJ, the rats were administered GJ 30 min before NFP; CJ, the rates were administered CJ 30 min before NFP. *$P < 0.05$, compared with the values in the group administered saline.

Furanocoumarin derivatives in CJ and GJ

No furanocoumarin derivative was observed in CJ. On the other hand, GJ contained three kinds of furanocoumarin derivatives, bergamottin, 6′,7′-dihydroxybergamottin and bergaptol (6.3, 3.4 and 9.5 μg mL^{-1}, respectively).

Discussion

Effects of CJ on NFP oxidation in human liver microsomes

CYP3A4, or NFP oxidase, is a major enzyme for NFP oxidation and is mainly expressed in human small intestine as well as human liver (Kolars et al 1992). An experiment using human liver microsomes was therefore carried out in order to investigate whether or not CJ induces drug interaction in humans in vitro (Figure 1A). The results showed that CJ as well as GJ caused significant inhibition of NFP oxidation activity during preincubation with NADPH. NADPH is an essential cofactor of mechanism-based inhibition with furanocoumarin derivatives of P450 activities (He et al 1998; Koenigs & Trager 1998). The results therefore indicate that component(s) in CJ cause a mechanism-based inhibition during CYP oxidation. Most recently, inhibition of human CYP3A-catalysed midazolam 1′-hydroxylation activity by commercial fruit juices, including pomegranate, black raspberry, black mulberry and wild grape juice, as well as GJ during preincubation with NADPH was also reported (Kim et al 2006). Thus we discovered that a component or components present in CJ inhibit human CYP3A-mediated metabolism of NFP. That is, our results show that CJ may affect the pharmacokinetics of CYP3A-mediated drugs.

Effects of CJ on NFP pharmacokinetics

We constructed a system to evaluate interactions between NFP and fruit juice in rats in vivo. In the previous studies, the AUC of NFP was increased significantly by i.d. administration of GJ (Mohri et al 2000) but not orange juice (Mohri & Uesawa 2001b) and sweetie juice (Uesawa & Mohri 2005b), as compared with saline. Our pharmacokinetic analyses demonstrated that GJ caused increased gastrointestinal absorption of NFP in rats. It was thought that NFP oxidation by CYP3A in the intestinal mucosa was inhibited by GJ administration (Mohri et al 2000). Actually, microsomes from the rat small intestine indicated testosterone 6β-oxidation (Mohri & Uesawa 2001a), an index of CYP3A activity, as did microsomes from the human small intestine and liver (Fitzsimmons & Collins 1997). Furthermore, the rat studies with small intestinal microsomes clarified that bergamottin and 6′,7′-dihydroxybergamottin, furanocoumarin

derivatives in GJ, contributed to the inhibition of the NFP oxidation in rat small intestine (Mohri & Uesawa 2001b). These observations in rats were very similar to those found in humans (Lown et al 1997) and suggest that evaluation using rats is useful for predicting drug–food interactions in clinical settings. The present study therefore investigated the effect of CJ administration on NFP pharmacokinetics using rats. Injection of CJ into the duodenum 30 min before NFP administration affected the plasma concentration–time profile of NFP (Figure 2). The AUC and CL/F were significantly increased in the CJ preadministered group compared with the control group (1.64 and 0.61 times, respectively; Table 1). However, other pharmacokinetic parameters, such as MRT, were not changed. These observations are similar to those found after GJ injection (Figure 2, Table 1), that is CJ administration probably increases the small intestinal absorption of NFP, as does GJ administration.

Effects of CJ on NFP oxidation in rat small intestinal microsomes

Many of the drugs interacting with GJ serve as substrates for the phase I metabolic enzyme cytochrome P450 3A (CYP3A) and the drug elimination transport protein P-glycoprotein. Drug–GJ interaction is caused by the inhibition of both the CYP3A subfamily (Bailey et al 1998) and P-glycoprotein-mediated drug transport (Takanaga et al 1998; Edwards et al 1999) in the intestinal mucosa. It is reported that NFP is not a substrate for P-glycoprotein (Soldner et al 1999). It has therefore been suggested that the pharmacokinetic interaction of NFP CJ occurs only through inhibition of the CYP3A-mediated metabolism of the drug. The effects of CJ as well as GJ on NFP oxidation were investigated using microsomes from rat small intestine. As a result, CJ and GJ both showed significant potential inhibition dependent on preincubation with NADPH. These findings suggest that CJ, like GJ, includes substance(s) that suppress NFP oxidation by a mechanism-based inhibition.

Greenblatt et al (2006) showed that although CJ inhibited CYP2C9 activity in the in-vitro study, this effect was not seen in the clinical study. These findings suggest that, in vivo, the inhibitory component(s) of CJ does not pass from the intestinal tract to the liver. Thus reinforcement of the anticoagulant effect of warfarin with CJ intake, as seen in case reports (Suvarna et al 2003; Grant 2004), may depend on mechanisms unlike the CYP inhibition or the patients' idiosyncratic ability to lower the intestinal barrier to the inhibitory component(s) of CJ (Fromm 2002). A paper on the interaction between CJ and cyclosporine administered orally in humans has recently been published (Grenier et al 2006). This paper shows that CJ does not affect the pharmacokinetics of cyclosporine in humans. Because the oral bioavailability of cyclosporine is limited with intestinal CYP3A, as is also the case with nifedipine, this phenomenon is apparently inconsistent with our finding that CJ enhances the bioavailability of nifedipine administered intraduodenally in rats. That is, if CJ can inhibit the activity of intestinal CYP3A in humans, the AUC of cyclosporine administered with CJ increases compared with the control. We suggest that this contradiction may be explained as follows. (1) It may be due to species specificity, that is a major isoform belonging to the CYP3A subfamily in human intestine and liver is CYP3A4. On the other hand, CYP3A9 and CYP3A62 are expressed in male rat intestine (Matsubara et al 2004). In the present experiments with CJ using human liver microsomes, it was observed that CJ hardly inhibited the nifedipine oxidation activity of human liver microsomes in the condition with the preincubation without NADPH (Figure 1A). On the other hand, the activity of rat intestinal microsomes was strongly inhibited with CJ under the same condition (Figure 1B). Such a difference may contribute to the different sensitivities to CJ between rats and humans. (2) The difference of drugs may play a part. The drug used in the previously cited paper was cyclosporine. However, the interactions between the drug and GJ might be difficult to reproduce. Brunner et al (1998) reported that single intakes of GJ caused only a 5% increase in cyclosporine AUC; however, no significant effect was seen in other pharmacokinetic parameters. Cyclosporine might be less sensitive than nifedipine to the interaction. (3) The difference of CJ components may be important. CJ is produced from cranberry. Naturally, the constituents of CJ depend on the raw material and the manufacturing process. Discrepancies may therefore be due to the differences in the CJ brands used by the researchers.

It might be important in a clinical setting to specify whether patients who receive therapy with drugs metabolized by CYP3A drink CJ or GJ. Furthermore, our results suggest that inhibitor(s) are present in CJ as well as in GJ. Furanocoumarin derivatives in GJ, such as bergamottin and 6′,7′-dihydroxybergamottin, cause drug–GJ interactions because of the mechanism-based inhibition of CYP3A4 in the small intestine (Guo & Yamazoe 2004). However, no furanocoumarin was observed in our detection system. Recently Kim et al (2006) showed that a component(s) of mulberry is a mechanism-based inhibitor of human CYP3A in vitro. However, there is no report indicating the existence of furanocoumarins. It has been reported that anthocyanins in black mulberry show potent antioxidant activity (Liu et al 2004). It is supposed that anthocyanins in CJ might also be able to inhibit CYP oxidation. It might be worthwhile to identify the inhibitory component(s) in CJ because an understanding of the interaction might be useful in identifying and avoiding foods and drinks causing drug interactions due to the inhibition of the intestinal metabolism of drugs. Further investigations to identify and characterize such inhibitory component(s) are therefore necessary.

Conclusions

In conclusion, the present results demonstrate that NFP oxidation activities in rat intestinal and human hepatic microsomes are inhibited by preincubation with CJ. Furthermore, CJ increases the NFP concentration in rat plasma. These findings suggest that CJ might affect the plasma concentration of NFP in humans as well as in rats. Further investigations of the pharmacokinetic interaction between nifedipine and CJ are necessary in humans because humans and rats express different CYP3A isoforms.

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