Original Research Paper

Effects of tomato juice on the pharmacokinetics of CYP3A4-substrate drugs

CrossMark

*Atsuko Ohkubo [1], Tomomi Chida [2], Hidetomo Kikuchi, Tadashi Tsuda, Katsuyoshi Sunaga ***

Laboratory of Pharmacotherapy, Department of Clinical Dietetics and Human Nutrition, Faculty of Pharmaceutical Sciences, Josai University, Keyakidai 1-1, Sakado, Saitama 350-0295, Japan

ARTICLE INFO

ABSTRACT

We previously demonstrated that tomato juice (TJ) contains potent mechanism-based inhibitor(s) of CYP3A4. In this study, we investigated the effects of TJ and grapefruit juice (GFJ) on the pharmacokinetics of the CYP3A4-substrate drugs, nifedipine (NFP) and midazolam (MDZ), in male Wistar rats. Oral administration of GFJ 90 min before the intraduodenal administration of NFP or MDZ increased the area under the concentration–time curves (AUCs) of NFP and MDZ by 32.4% and 89.4%, respectively. TJ increased MDZ blood concentrations and AUC after intraduodenal MDZ administration; however, it had no effect on NFP. When MDZ and NFP were intravenously administered, GFJ significantly increased the AUC of MDZ, but only slightly increased that of NFP. In contrast, TJ only slightly increased the AUC of MDZ. These results suggest that, similar to GFJ, TJ influences the pharmacokinetics of CYP3A4-substrate drugs; however, it may be a drug-dependent partial effect.

© 2017 Shenyang Pharmaceutical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Many food and/or beverages have recently been found to influence drug metabolism and transport, sometimes resulting in clinically important drug interactions. These food–drug interactions are a critical aspect of pharmacotherapy, with potential impacts on the pharmacokinetics and pharmacodynamics of drugs. Pharmacokinetic interactions can involve enzymes and transporters that are involved in drug absorption,

---

distribution, metabolism, and excretion. Pharmacodynamic interactions involve the pharmacological effects of a drug or the physiologic effect of a dietary constituent [1].

Foods and beverages that inhibit cytochrome P450 (CYP) drug metabolism enzymes can elevate the blood concentrations of co-administered drugs, resulting in food–drug interactions with potentially adverse effects [2–4]. In vitro screening assays that have evaluated various food and beverages, including beer, red wine, black and herbal teas, garlic, spices, mace, nutmeg, fruits, and fruit juices, have shown the ability of these to inhibit enzyme-mediated drug metabolism [5–10]. In addition, several fruit juices have been reported to cause pharmacokinetic food–drug interactions in vivo, including grapefruit (GFJ) [11–14], orange [12], star fruit [15], pomelo [16], cranberry [17], and pomegranate juice [18].

Recently, we reported that tomato juice (TJ) extract contains potent mechanism-based inhibitor(s) of CYP3A4 similar to GFJ [19]. However, whether TJ can alter the pharmacokinetic profile of CYP3A-substrate drugs remains unknown.

TJ is a very popular beverage; epidemiological studies have indicated that high consumption of tomato products is related to the reduced risk of prostate cancer [20,21]. Lycopene, a major ingredient in tomato, shows promising anticancer effects, including antioxidant activity, inhibition of cell cycle progression, apoptosis induction, increased gap-junctional cell communication, inhibition of insulin-like growth factor I signal transduction, and inhibition of androgen activation and signaling [22,23]. Furthermore, it has recently been reported that a conjugated linoleic acid (CLA) derivative, 9-oxo-10,12-octadecadienoic acid (9-oxo-ODA) [24], which is present in fresh tomato fruit, and 13-oxo-9,11-octadecadenoic acid (13-oxo-ODA) [25], which is an isomer of 9-oxo-ODA and present in only TJ but not in fresh tomato fruit, both serve as PPARa agonists. These reports suggest that 13-oxo-ODA is a more potent PPARa agonist than 9-oxo-ODA, and may improve obesity-induced dyslipidemia and hepatic steatosis.

To date, no studies have investigated whether TJ can cause adverse food–drug interactions in vivo. In this study, we evaluated the potential of TJ to influence the disposition of drugs that are metabolized by CYP3A4, such as nifedipine (NFP) and midazolam (MDZ).

2. Materials and methods

2.1. Materials

NFP was purchased from Sigma-Aldrich (MO, USA). MDZ was purchased from Wako Pure Chemical Ind., Ltd. (Osaka, Japan). Acetonitrile was purchased from Kanto Chemical (Tokyo, Japan) and was used for high performance liquid chromatography. All other reagents were of analytical grade.

2.2. Test samples

Additive-free TJ was purchased from Ito En Ltd. (Tokyo, Japan). Grapefruits (Citrus paradisi Macf.) were obtained from local commercial sources. Minced fresh grapefruit (without epicarp) was homogenized with an AM-8 homogenizer (Nihon Seiki Co., Ltd., Tokyo, Japan).

2.3. Animal experiments

Eight-week-old (180–200 g) male Wistar rats (Sankyo Labo Service Co., Tokyo, Japan) were given free access to water and a normal laboratory diet (MF, Oriental Yeast Co., Tokyo, Japan). All animals were acclimatized for 1 week and maintained in a room with controlled temperature (23 ± 3 °C), humidity (55 ± 10%), and a 12 h day/night cycle. All animal studies were performed in accordance with the "Standards Relating to the Care and Management of Experimental Animals" (Notice No. 6 of the Office of Prime Minister, dated March 27, 1980) and the guidelines of the Institutional Animal Care and Use Committee at the Josai University Life Science Center.

2.4. Pharmacokinetic studies

Rats were fasted overnight before experiments. For pharmacokinetic studies, rats were anesthetized with 20% urethane (1 g/kg body weight, intraperitoneally) 60 min after treatment with peroral administration (p.o.) of TJ, GFJ, or water. NFP (3 mg/kg/ml) or MDZ (20 mg/kg/ml) were then administered 30 min later via the duodenum or femoral vein. Blood samples (0.2 ml) were collected via the jugular vein at 2.5, 5, 10, 15, 30, 60, 90, 120, 180, and 240 min for intraduodenal administration (i.d.) or at 1, 5, 10, 30, 60, 90, 120, 180, and 240 min for intravenous administration (i.v.). Samples were immediately centrifuged at 15,000 rpm (4 °C) for 5 min, and plasma was separated. Plasma samples were stored at –40 °C until analysis.

2.5. HPLC analysis of NFP and MDZ

A 25-μl aliquot of each thawed plasma sample was transferred into a new tube with 50 μl acetonitrile containing internal standard (100 ng methylparaben for NFP, 100 ng diazepam for MDZ). After vigorous mixing, samples were centrifuged at $15,000 \times g$ for 10 min at 4 °C. The supernatant (20 μl) was directly injected into the HPLC system, which consisted of a PU2089 pump, UV2075 UV absorbance detector, an AS2057 auto injector, and a ChromNAV system controller (JASCO). For NFP, the HPLC conditions included a Myghtysil RP-18GP column (5 μm, 4.6 mm × 250 mm; Kanto Chemical Co., Tokyo, Japan) connected to a precolumn (5 μm, 2 × 5 mm; Kanto Chemical Co, Tokyo, Japan), and eluted at a flow rate of 1.0 ml/min with a mobile phase of acetonitrile: 10 mM sodium phosphate [pH 6.1; 45:55 (v/v)]. Detection of NFP was performed by analyzing the UV absorbance at 236 nm. The retention time was 12.5 min for NFP and 5.4 min for methylparaben. For MDZ, the HPLC conditions included a Myghtysil RP-18GP column (5 μm, 4.6 mm × 150 mm; Kanto Chemical Co., Tokyo, Japan) connected to a precolumn (5 μm, 2 mm × 5 mm; Kanto Chemical Co, Tokyo, Japan), and eluted at a flow rate of 1.0 ml/min with a mobile phase of acetonitrile:10 mM sodium acetate [pH 4.7; 45:55 (v/v)]. Detection was performed by analyzing the UV absorbance at 220 nm. The retention time was 6.5 min for MDZ and 9.4 min for diazepam.

2.6. Data analysis

The blood concentration–time profile data (0–4 h) from each rat was analyzed by a model-independent method using the

MULTI computer program [26]. We obtained following parameters: peak time (T_{max}), maximum concentration (C_{max}), elimination rate constant (k_{el}), area under the curve (AUC), mean residence time from zero to infinity (MRT), elimination half-life ($t_{1/2}$), total clearance (CL_{tot}), and volume of distribution (V_d). The oral bioavailability (F) was calculated using $AUC_{p.o}/AUC_{i.v.}$. Statistical differences between the treatment and control groups were evaluated using Dunnett's test; a P value of <0.05 was considered significant.

3. Results and discussion

We have previously found that TJ extract contains potent mechanism-based inhibitor(s) of CYP3A4 similar to those of GFJ [19]. This study investigated whether TJ affects CYP3A4-substrate drug disposition *in vivo*. We employed two CYP3A4 substrate drugs NFP and MDZ to judge whether TJ influenced the pharmacokinetics of CYP3A4-substrate drugs compared with that of water, and the results were compared to those of GFJ.

3.1. Dosage of NFP, MDZ, and test samples

The doses of NFP [14,27] and MDZ [28,29] are similar to the doses used in previous studies on *in vivo* pharmacokinetics in rats. These doses can sufficiently detect plasma drugs by the HPLC method. In addition, we used 5 ml/kg dose of TJ, GFJ, and water in this study. This dose was appropriate as it corresponds to an intake of 300–400 ml for persons weighing 60–80 kg.

3.2. Effects of GFJ on intraduodenally administered NFP and MDZ pharmacokinetics

When GFJ (5 ml/kg) was orally administered 90 min before intraduodenal administration of NFP (3 mg/kg) or MDZ (20 mg/kg), the area under the concentration–time curve (AUC) of NFP (Fig. 1A and Table 1) and MDZ (Fig. 2A and Table 2) increased by 30.3% and 58.1%, respectively, compared with that of water. Consequently, GFJ significantly increased both the blood concentrations and AUC of intraduodenally administered NFP and MDZ. These findings were identical to those of previous reports [14,30].

3.3. Effects of TJ on intraduodenally administered NFP and MDZ pharmacokinetics

In contrast, TJ increased the MDZ blood concentrations and the AUC by 73.0% (Fig. 2B and Table 4) compared with water but did not influence NFP blood concentration and parameters (Fig. 1B and Table 3). These results demonstrate that TJ has the potential to influence the pharmacokinetics of some CYP3A4-substrate drugs in rats, similar to the findings for GFJ.

However, TJ did not influence the pharmacokinetics of NFP and MDZ to the same extent as GFJ did. The reasons for this
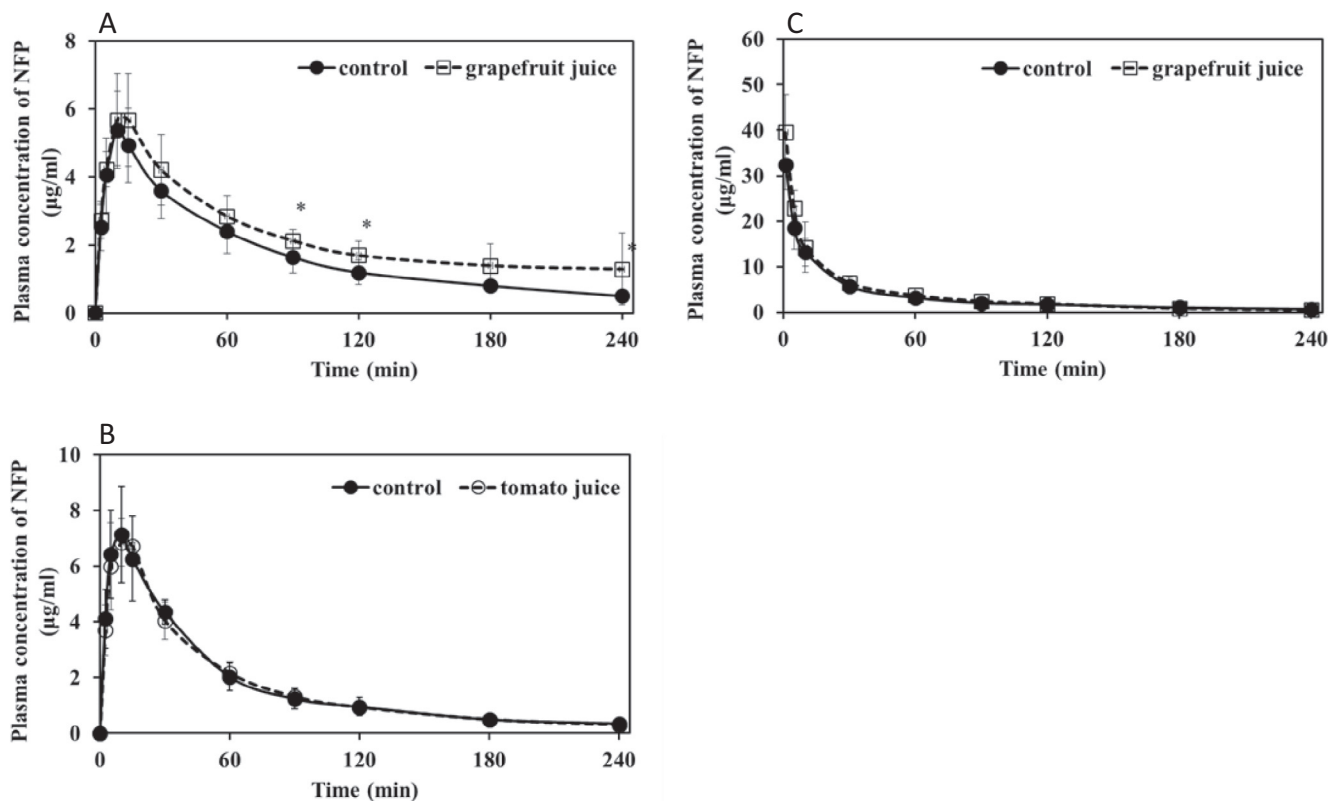
Fig. 1 – Plasma concentration–time profiles of rats treated with 3 mg/kg nifedipine 90 min after a single exposure to TJ, GFJ, or water (5 ml/kg, p.o.). A and B, intraduodenal administration; C, intravenous administration. Each point and bar represents the mean and SD of five or six rats. *P < 0.05 compared to control values.

Table 1 – Pharmacokinetic parameters of intraduodenally and intravenously administered NFP after pre-treatment GFJ or water.

	I.D. administration		I.V. administration	
	Control	GFJ	Control	GFJ
T_{max} (h)	0.17 ± 0.02	0.20 ± 0.04	-	-
C_{max} (µg/ml)	5.30 ± 1.14	5.92 ± 1.48	-	-
K_{el} (h^{-1})	0.50 ± 0.11	0.42 ± 0.20	0.57 ± 0.25	0.58 ± 0.07
AUC (µg/ml · h)	6.87 ± 1.61	8.95 ± 1.65[a]	11.6 ± 0.76	13.7 ± 1.59
MRT (h)	1.27 ± 0.07	1.37 ± 0.36	0.91 ± 0.18	0.76 ± 0.22
$t_{1/2}$ (h)	1.44 ± 0.31	1.95 ± 1.05	1.35 ± 0.58	1.21 ± 0.16
CL_{tot} (ml/h/kg)	0.12 ± 0.02	0.09 ± 0.02	0.07 ± 0.02	0.06 ± 0.02
V_d (ml/kg)	0.21 ± 0.02	0.21 ± 0.04	0.09 ± 0.20	0.08 ± 0.02
F (%)	59.2	65.3	——	——

Data represent means ± SD ($n = 5$–6).
[a] $P < 0.05$ compared to control values.

Table 2 – Pharmacokinetic parameters of intraduodenally and intravenously administered MDZ after pre-treatment with GFJ or water.

	I.D. administration		I.V. administration	
	Control	GFJ	Control	GFJ
T_{max} (h)	0.49 ± 0.21	0.50 ± 0.00	-	-
C_{max} (µg/ml)	1.66 ± 0.64	2.53 ± 1.04	-	-
K_{el} (h^{-1})	0.44 ± 0.23	0.32 ± 0.14	0.53 ± 0.29	0.44 ± 0.07
AUC (µg/ml·h)	2.72 ± 0.79	4.30 ± 1.25[a]	10.5 ± 2.80	13.5 ± 1.31[a]
MRT (h)	1.34 ± 0.28	1.56 ± 0.08	0.85 ± 0.13	0.99 ± 0.09
$t_{1/2}$ (h)	2.35 ± 1.41	2.13 ± 0.64	1.52 ± 0.74	1.61 ± 0.27
CL_{tot} (ml/h/kg)	0.20 ± 0.08	0.15 ± 0.07	0.09 ± 0.02	0.07 ± 0.007[a]
V_d (ml/kg)	0.61 ± 0.36	0.61 ± 0.31	0.13 ± 0.25	0.03 ± 0.009
F (%)	26.0	31.8	——	——

Data represent means ± SD ($n = 5$–6).
[a] $P < 0.05$ compared to control values.

are not clear; however, differences in oral bioavailability (Tables 1, 2, and 4) of NFP (59.2%) and MDZ (26.0%–26.1%) may be a contributing factor. It has previously been reported that single-strength GFJ significantly increases the plasma concentrations of NFP in rats [14]. On the other hand, there is a report that while concentrated GFJ ($2 \times$ concentrations) significantly increases NFP bioavailability in rats, regular strength GFJ has no significant effect on NFP bioavailability [31]. Furthermore, it has been reported that pre-dosing with the GFJ constituent bergamottin increases the plasma level of diazepam, a substrate

of CYP3A4 and CYP2C9 in male beagle dogs, but not in rats, indicating that the rat may not be an appropriate model [32]. In this study, these factors may have contributed to our findings that TJ did not influence NFP disposition. However, more research should be warranted.

The clinical significance of CYP3A4 inhibition by TJ is not well understood. In one study in which TJ was used as a 'vehicle', it was reported that TJ does not influence the pharmacokinetics of the proton pump inhibitor lansoprazole [33]. However, this is likely due to the fact that the study was not
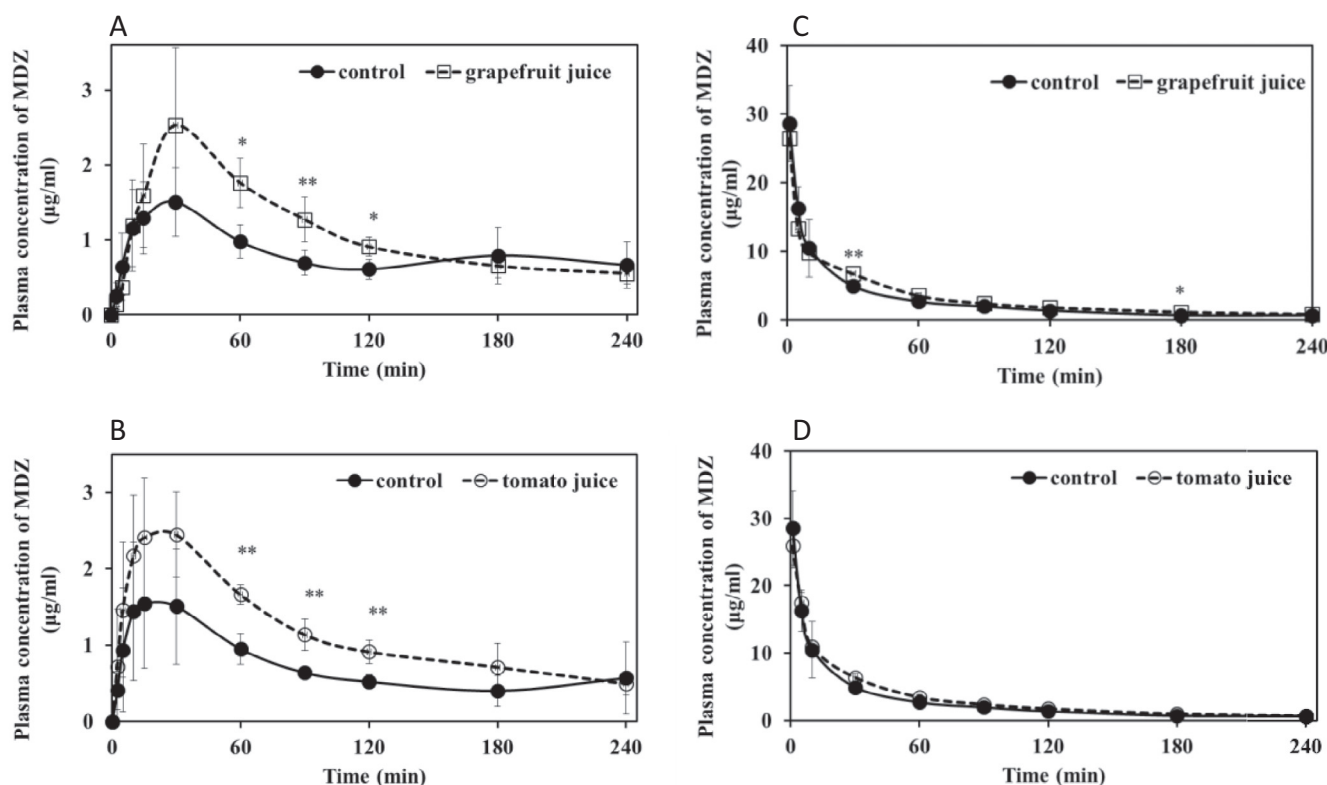

Fig. 2 – Plasma concentration–time profiles of rats treated with 20 mg/kg midazolam 90 min after a single exposure to TJ, GFJ, or water (5 ml/kg, p.o.). A and B, intraduodenal administration; C and D, intravenous administration. Each point and bar represents the mean and SD of five or six rats. **$P < 0.01$, *$P < 0.05$ compared to control values.

Table 3 – Pharmacokinetic parameters of intraduodenally administered NFP after pre-treatment with TJ or water.

| | I.D. administration | |
	Control	TJ
T_{max} (h)	0.17 ± 0.04	0.17 ± 0.04
C_{max} (µg/ml)	7.21 ± 1.65	6.97 ± 0.83
K_{el} (h^{-1})	0.62 ± 0.14	0.59 ± 0.07
AUC (µg/ml·h)	6.64 ± 1.68	6.72 ± 0.92
MRT (h)	0.95 ± 0.15	0.99 ± 0.07
$t_{1/2}$ (h)	1.16 ± 0.23	1.18 ± 0.13
CL_{tot} (ml/h/kg)	0.15 ± 0.04	0.14 ± 0.02
V_d (ml/kg)	0.17 ± 0.02	0.17 ± 0.02

Data represent means ± SD ($n = 5$–6).

Table 4 – Pharmacokinetic parameters of intraduodenally and intravenously administered MDZ after pre-treatment with TJ or water.

| | I.D. administration | | I.V. administration | |
	Control	TJ	Control	TJ
T_{max} (h)	0.43 ± 0.13	0.40 ± 0.34	-	-
C_{max} (µg/ml)	1.70 ± 0.67	2.76 ± 0.96	-	-
K_{el} (h^{-1})	0.46 ± 0.07	0.38 ± 0.34	0.53 ± 0.29	0.56 ± 0.11
AUC (µg/ml·h)	2.74 ± 1.05	4.74 ± 0.29^a	10.5 ± 2.80	12.8 ± 1.21
MRT (h)	1.44 ± 0.18	1.35 ± 0.42	0.85 ± 0.13	0.98 ± 0.04
$t_{1/2}$ (h)	2.56 ± 0.34	1.86 ± 1.99	1.52 ± 0.74	1.29 ± 0.34
CL_{tot} (ml/h/kg)	0.21 ± 0.04	0.17 ± 0.11	0.09 ± 0.02	0.07 ± 0.009
V_d (ml/kg)	0.68 ± 0.11	0.42 ± 0.49	0.13 ± 0.2	0.09 ± 0.004
F (%)	26.1	37.0	——	——

Data represent means ± SD ($n = 5$–6).
^{a} $P < 0.01$ compared to control values.

specifically designed to evaluate the inhibitory effect of TJ on CYP3A. In addition, lansoprazole is not an established CYP3A probe substrate, and the tomato juice product used was not characterized prior to use. The possibility of a food–drug interaction between tomato juice and appropriate CYP3A substrates needs further examination in clinical studies.

3.4. Effects of TJ and GFJ on intravenously administered NFP and MDZ pharmacokinetics

Another interesting result of our study was that when GFJ (5 ml/kg) was orally administered 90 min before the intravenous administration of MDZ (20 mg/kg), GFJ significantly increased the AUC of MDZ by 28.6% and that the systemic clearance (CL_{tot}) of MDZ decreased by 25.0% compared with the oral administration of water (Fig. 2C and Table 2), but had no effect on NFP (Fig. 1C and Table 1). In comparison, TJ slightly increased the AUC (22.0%) of intravenously administered MDZ (Fig. 2D and Table 4); however, this effect was not significant. In the case of TJ, pharmacokinetic study of NFP by intravenous injection was not conducted because there was no difference in the elimination process in duodenal administration. However, these results demonstrate the possibility that GFJ and possibly TJ influenced not only the bioavailability but also the elimination of these drugs (i.e., GFJ and TJ inhibit not

only intestinal but also hepatic drug metabolism). On the other hand, several studies have suggested that GFJ selectively inhibits intestinal CYP3A4, as opposed to hepatic CYP3A4 [34–36]. Thus, GFJ reportedly did not alter the pharmacokinetics of CYP3A4 substrates administered intravenously [30,37], and little change in the elimination half-life was observed when the drugs were administered orally [37,38]. On the other hand, it has been reported that the consumption of one glass of double-strength GFJ three times a day for 3 d significantly increases the AUC, C_{max}, and $t_{1/2}$ of MDZ and reduces the erythromycin breath test value [39]. These observations indicate that high doses of GFJ may inhibit both intestinal and hepatic CYP3A4 *in vivo*. In this study, appropriate experimental techniques and selection of MDZ as CYP3A substrate drug may have obtained high precision results. Further investigation is required to clarify whether GFJ and TJ influence the liver drug-metabolizing enzymes.

4.   Conclusions

TJ increased MDZ blood concentrations and the AUC after intraduodenal MDZ administration similar to GFJ. Although it remains unclear why TJ did not influence NFP disposition in rats, it cannot be denied that TJ influences the pharmacokinetics of other CYP3A4 substrates in humans. In future studies, factors underlying the variability of TJ in influencing the pharmacokinetics of CYP3A4 substrates should be investigated, particularly for humans in order to perform inter-species comparisons.

Acknowledgements

Conflicts of interest

The authors declare that there is no conflicts of interest.

REFERENCES

[1] Boullata JI. An introduction to drug-nutrient interactions. In: Boullata JI, Armenti VT, editors. Handbook of drug-nutrient interactions. New York: Humana Press; 2010. p. 3–26.

[2] Spence JD. Drug interactions with grapefruit: whose responsibility is it to warn the public? Clin Pharmacol Ther 1997;61:395–400.

[3] Dresser GK, Bailey DG, Carruthers SG. Grapefruit juice–felodipine interaction in the elderly. Clin Pharmacol Ther 2000;68:28–34.

[4] Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. Neurology 2004;62:670.

[5] Foster BC, Vandenhoek S, Hana J, et al. In vitro inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products. Phytomedicine 2003;10:334–342.

[6] Sand PG, Dreiseitel A, Stang M, et al. Cytochrome P450 2C19 inhibitory activity of common berry constituents. Phytother Res 2010;24:304–307.

[7] Kimura Y, Ito H, Hatano T. Effects of mace and nutmeg on human cytochrome P450 3A4 and 2C9 activity. Biol Pharm Bull 2010;33:1977–1982.

[8] Fujita T, Kawase A, Niwa T, et al. Comparative evaluation of 12 immature citrus fruit extracts for the inhibition of cytochrome P450 isoform activities. Biol Pharm Bull 2008;31:925–930.

[9] MacDonald L, Foster BC, Akhtar H. Food and therapeutic product interactions – a therapeutic perspective. J Pharm Pharm Sci 2009;12:367–377.

[10] Hidaka M, Fujita K, Ogikubo T, et al. Potent inhibition by star fruit of human cytochrome P450 3A (CYP3A) activity. Drug Metab Dispos 2004;32:581–583.

[11] Bailey DG, Malcolm J, Arnold O, et al. Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998;46:101–110.

[12] Di Marco MP, Edwards DJ, Wainer IW, et al. The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. Life Sci 2002;71:1149–1160.

[13] Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs 2004;4:281–297.

[14] Mohri K, Uesawa Y. Effects of furanocoumarin derivatives in grapefruit juice on nifedipine pharmacokinetics in rats. Pharm Res 2001;18:177–182.

[15] Hidaka M, Okumura M, Ogikubo T, et al. Transient inhibition of cyp3a in rats by star fruit juice. Drug Metab Dispos 2006;34:343–345.

[16] Grenier J, Fradette C, Morelli G, et al. Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans. Clin Pharmacol Ther 2006;79:255–262.

[17] Uesawa Y, Mohri K. Effects of cranberry juice on nifedipine pharmacokinetics in rats. J Pharm Pharmacol 2006;58:1067–1072.

[18] Voruganti S, Yamsani SK, Ravula SK, et al. Effect of pomegranate juice on intestinal transport and pharmacokinetics of nitrendipine in rats. Phytother Res 2012;26:1240–1245.

[19] Sunaga K, Ohkawa K, Nakamura K, et al. Mechanism-based inhibition of recombinant human cytochrome P450 3A4 by tomato juice extract. Biol Pharm Bull 2012;35:329–334.

[20] Giovannucci E, Rimm EB, Liu Y, et al. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 2002;94:391–398.

[21] Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev 2004;13:340–345.

[22] Sharoni Y, Danilenko M, Dubi N, et al. Carotenoids and transcription. Arch Biochem Biophys 2004;430:89–96.

[23] Wertz K, Siler U, Goralczyk R. Lycopene: modes of action to promote prostate health. Arch Biochem Biophys 2004;430:127–134.

[24] Kim YI, Hirai S, Takahashi H, et al. 9-oxo-10(E),12(E)-Octadecadienoic acid derived from tomato is a potent PPAR alpha agonist to decrease triglyceride accumulation in mouse primary hepatocytes. Mol Nutr Food Res 2011;55:585–593.

[25] Kim YI, Hirai S, Goto T, et al. Potent PPARalpha activator derived from tomato juice, 13-oxo-9,11-octadecadienoic acid, decreases plasma and hepatic triglyceride in obese diabetic mice. PLoS ONE 2012;7:e31317.

[26] Yamaoka K, Nakagawa TA. nonlinear least squares program based on differential equations, MULTI (RUNGE), for microcomputers. J Pharmacobiodyn 1983;6:595–606.

[27] Mohri K, Uesawa Y, Sagawa K. Effects of long-term grapefruit juice ingestion on nifedipine pharmacokinetics: induction of rat hepatic P-450 by grapefruit juice. Drug Metab Dispos 2000;28:482–486.

[28] Zhang W, Tan TM, Lim LY. Impact of curcumin-induced changes in P-glycoprotein and CYP3A expression on the pharmacokinetics of peroral celiprolol and midazolam in rats. Drug Metab Dispos 2007;35:110–115.

[29] Li WL, Xin HW, Su MW. Inhibitory effects of continuous ingestion of Schisandrin A on CYP3A in the rat. Basic Clin Pharmacol Toxicol 2012;110:187–192.

[30] Kupferschmidt HH, Ha HR, Ziegler WH, et al. Interaction between grapefruit juice and midazolam in humans. Clin Pharmacol Ther 1995;58:20–28.

[31] Grundy JS, Eliot LA, Kulmatycki KM, et al. Grapefruit juice and orange juice effects on the bioavailability of nifedipine in the rat. Biopharm Drug Dispos 1998;19:175–183.

[32] Sahi J, Reyner EL, Bauman JN, et al. The effect of bergamottin on diazepam plasma levels and P450 enzymes in beagle dogs. Drug Metab Dispos 2002;30:135–140.

[33] Chun AH, Erdman K, Chiu YL, et al. Bioavailability of lansoprazole granules administered in juice or soft food compared with the intact capsule formulation. Clin Ther 2002;24:1322–1331.

[34] Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997;99:2545–2553.

[35] Wu CY, Benet LZ, Hebert MF, et al. Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. Clin Pharmacol Ther 1995;58:492–497.

[36] Ameer B, Weintraub RA. Drug interactions with grapefruit juice. Clin Pharmacokinet 1997;33:103–121.

[37] Ducharme MP, Warbasse LH, Edwards DJ. Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. Clin Pharmacol Ther 1995;57:485–491.

[38] Bailey DG, Arnold JM, Bend JR, et al. Grapefruit juice-felodipine interaction: reproducibility and characterization with the extended release drug formulation. Br J Clin Pharmacol 1995;40:135–140.

[39] Veronese ML, Gillen LP, Burke JP, et al. Exposure-dependent inhibition of intestinal and hepatic CYP3A4 in vivo by grapefruit juice. J Clin Pharmacol 2003;43:831–839.