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

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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.

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,

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Abbreviations: TJ, tomato juice; GFJ, grapefruit juice; NFP, nifedipine; MDZ, midazolam; AUC, area under the concentration–time curve; CYP, cytochrome P450; 9-oxo-ODA, 9-oxo-10,12-octadecadienoic acid; 13-oxo-ODA, 13-oxo-9,11-octadecadenoic acid.
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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 × *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