Interactions of grapefruit juice and cardiovascular medications: A potential risk of toxicity

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GE Lim, T Li, HS Buttar. Interactions of grapefruit juice and cardiovascular medications: A potential risk of toxicity. Exp Clin Cardiol 2003;8(2):99-107.

Recently, drug interactions with grapefruit juice (GFJ) have received considerable attention from basic scientists, physicians, industry and drug regulatory agencies. GFJ has been shown to inhibit cytochrome P-450 3A4 isoenzyme and P-glycoprotein transporters in the intestine and liver. The GFJ-induced inhibitory effects are considered to be responsible for alterations in drug bioavailability, and pharmacokinetic and pharmacodynamic changes when drugs are ingested concurrently with GFJ. However, little or no interaction is observed when GFJ is taken concomitantly with parentally administered drugs. It is well known that risk factors for cardiovascular disease increase with advancing age, while hepatic metabolic activity decreases in elderly individuals. It is, therefore, possible that the combination of GFJ and cardiovascular medications may pose a health risk, especially in elderly patients. A number of studies have shown interactions of GFJ with cardiovascular drugs such as calcium-channel blockers, angiotensin II receptor antagonists, beta-blockers, and statins. Such interactions are likely to change the pharmacokinetics and pharmacodynamics of these drugs, consequently causing undesirable health effects. Therefore, health care professionals and the public need to be advised of the potential risks associated with the concomitant use of GFJ and interacting medications, especially cardiovascular drugs and agents with a narrow therapeutic index. This review focuses on the adverse interactions of GFJ and cardiovascular medications, and the proposed underlying mechanisms of such interactions.

Key Words: *Cardiovascular drugs; Cytochrome P-450 3A4; Grapefruit juice; Interactions; P-glycoprotein*

Grapefruit juice (GFJ) is a commonly used beverage in North America and several brands are currently available for consumers. It has been estimated that in the year 2000, Canadians consumed 0.98 kg/year of GFJ per capita while orange juice consumption was 14.45 kg/year per capita (1). In 1997, a similar trend was observed in which 20% of US households purchased GFJ while 80% purchased orange juice (2).

GFJ is a rich source of vitamins A and C, and a good source of fibre. It is naturally fat- and cholesterol-free, and low in calories. Owing to these nutritional characteristics, the American Heart Association encourages consumption of GFJ as part of a routine heart-healthy diet. This endorsement motivates most people to consume fresh grapefruit or GFJ, given that cardiovascular disease is a prime killer worldwide (2).

Recently, there have been numerous reports of adverse interactions of GFJ with a wide variety of drugs. These interactions prompted Health Canada to issue an Advisory to inform the public and health care providers of possible risks associated with the concomitant use of GFJ and a variety of prescription medications. It has been reported that simultaneous ingestion of GFJ with certain cardiovascular medications may lead to increased bioavailability, and depending on the drug class or type, elevated blood levels may lead to serious adverse consequences. Essentially, all reported interactions result in pharmacokinetic changes, and the risks related to the simultaneous consumption of drugs with GFJ may be seen as an overdose of a particular medication (3). The clinical relevance of GFJ–drug interactions has recently been brought into the forefront, and several review papers have appeared in the literature indicating that a wide variety of drugs may interact with GFJ (3-5). Although tangelos, a hybrid of grapefruit and tangerine, may also interfere with the biotransformation of drugs, most other citrus fruits such as lemons, limes, citrons, naturally sweet oranges and tangerines are considered safe.

Bailey et al (6) accidentally discovered the interactive action of GFJ in 1989. The effects of ethanol on the hemodynamic effects of felodipine, a calcium-channel blocker, were being studied, and GFJ was chosen to mask the presence of ethanol to make it more palatable to the subjects. In 10 healthy male participants, consumption of ethanol (0.75 g/kg lean body weight) produced changes in the hemodynamic effects of felodipine, but it did not alter felodipine's bioavailability; instead, the plasma concentrations of felodipine were significantly altered by GFJ, the masking vehicle of alcohol (6).

Several studies have shown that GFJ inhibits the activity of both cytochrome P-450 3A4 ($CYP_{450}3A4$) and P-glycoprotein (P-gp). Juice extracted from Seville oranges also shows similar interactive effects with drugs as observed with GFJ (7), and juice extracted from pomelos also exhibits similar interactive properties (8). Juices extracted from limes, lemons, or commonly sold oranges do not exhibit similar interactive properties as noted with GFJ, Seville orange juice, sweetie juice and pomelo juice. Commercial confectioneries and preserves that contain grapefruit should also be used with caution because of the presence of the active ingredients responsible for the interactive effects (9).

In most studies, GFJ was given in either single or double doses over a three- to five-day period to ensure that there was an adequate amount of GFJ in the stomach and intestines to produce a significant effect. However, a recent study found

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that only one glass of GFJ is required to detect a significant effect. Lundahl et al (10) showed that a single glass of normal-strength GFJ was able to cause increases in the maximal plasma concentration (C_{max}) and half-life of felodipine in 14 subjects. If a physician is made aware that a patient is taking GFJ daily, adjustments to drug dosages should be made to achieve optimal therapy and to prevent any serious adverse effects. Alternately, patients should be advised to avoid the consumption of GFJ, because as little as one glass of GFJ (8 ounces or 250 mL) can interfere with drug metabolism and can lead to serious or even life-threatening adverse reactions.

The exact constituent(s) of GFJ responsible for the inhibitory activities of $CYP_{450}3A4$ and P-gp have not yet been conclusively identified. It was previously thought that flavonoids such as naringin or naringenin were the main biologically active components in GFJ, but Edwards and Bernier (11) have reported that a naringin solution diluted with GFJ had little influence on increasing the serum levels and bioavailability of testosterone, while a naringenin solution had virtually no effect on the disposition of this hormone. A recent study demonstrated that the amounts of naringin and naringenin in GFJ were too small to produce any inhibitory action on $CYP_{450}3A4$ activity (12).

It now appears that furanocoumarin derivatives are responsible for the enzyme inhibitory action of GFJ (8,13). In vitro experiments showed that 6',7'-dihydroxybergamottin (DHB) is the major furanocoumarin present in GFJ (14), but a recent study has suggested that another furanocoumarin, bergapten (5-methoxypsoralen), may be responsible for most of the enzymatic inhibitory action of GFJ (15). Further studies are required to determine the chemical nature of inhibitory compounds contained in GFJ because controversy about the active ingredients remains unresolved.

Bourian et al (16) observed high inter-subject variability in the metabolic disposition of GFJ. By giving 1.0 L of GFJ with coumarin to 18 healthy subjects, there was high variability in the renal excretion of GFJ-inhibitory components. There were also differences in the recovery of coumarin's primary metabolite, 7-hydroxycoumarin among the treated subjects (16). This study demonstrated that all individuals may not respond in the same manner to GFJ's interactive effects.

The purpose of this review is to summarize reported interactions of GFJ with cardiovascular medications, the potential risks associated with such interactions, as well as the molecular mechanisms involved in GFJ-drug interactions. Efforts shall also be made to highlight the actions being taken by drug regulatory agencies to increase awareness among the general public and health care professionals regarding GFJ-drug interactions and associated health risks. Interactions between GFJ and a wide variety of drugs such as antipsychotics, immunosuppressants, antibiotics, antidepressants and human immunodeficiency virus (HIV) therapies have also been reported, and further studies are required to properly assess the clinical implications of these interactions. Combined administration of cyclosporine and terfenadine with GFJ has been documented to increase serum levels of these drugs (17,18).

Because cardiovascular medications are often used by elderly patients, this subgroup may be at a higher risk than the younger populations due to compromised drug metabolism that is associated with age. It is well documented that hepatic enzyme activity is reduced in the elderly, and this reduction would influence drug pharmacokinetics and disposition. Results of an in vitro experiment showed that the hepatic activity of $CYP_{450}3A4$ decreases with age, and there is also a significant reduction in the number of proteins expressed in the liver with advancing age (19). Aside from a reduction in $CYP_{450}3A4$ isoenzymes, advancing age has shown to decrease hepatic blood flow, thereby increasing the amount of time a drug will spend in the systemic circulation and reducing clearance of the drug (20). In view of these observations, GFJ and any cardiovascular medication, especially those with narrow therapeutic margins, should never be administered concomitantly due to possible adverse interactions.

POSTULATED MECHANISMS OF GFJ-DRUG INTERACTIONS

While the exact underlying mechanism(s) remain to be elucidated, two mechanisms for the interaction between GFJ and a number of cardiovascular medications have been proposed. To ascertain which mechanism is operational, it is important to determine if the drug molecule is a substrate of either mechanism.

Inhibition of cytochrome P-450 enzymes

The cytochrome P-450 (CYP) system is intrinsic to all mammalian species and refers to an enzymatic system responsible for the biotransformation of xenobiotics into different metabolites. Many families of the cytochrome P-450 system have been recognized in various organisms, but 19 cytochrome P-450 families have been identified in humans. Only CYP-1, -2 and -3 are involved in the metabolism of currently used drugs, whereas nine families of CYP are involved in the metabolism of endogenous products produced by the body (21). Within each family, there are numerous isoforms that have similar structural and genomic properties such as $CYP_{450}3A4$ and $CYP_{450}3A5$. Both isoforms belong to the $CYP_{450}3A$ family, but there are significant differences in the amino acid sequence and structure that give each isoform its unique function and substrate specificity. Of all the marketed drugs, it has been shown that roughly 60% of them are metabolized by the $CYP_{450}3A4$ system (22-24). $CYP_{450}3A4$ is primarily found at three body sites such as the liver, intestine and kidneys (24). Although the concentration of $CYP_{450}3A4$ varies in different organs, its highest concentration is in the liver, followed by the jejeunum and colon, and the kidneys. The presence of the cytochrome P-450 system in enterocytes and hepatocytes contributes to the first-pass effect that accompanies the oral delivery of drugs. Substrates of the P-450 system may experience a decreased systemic concentration due to extensive metabolism of a drug by the intestinal wall before it is absorbed and enters the systemic circulation. Many drugs are known inhibitors of $CYP_{450}3A4$, and medications such as erythromycin, indinavir and ketoconazole exhibit reversible inhibition of $CYP_{450}3A4$ (22).

It has been demonstrated that simultaneous ingestion of GFJ inhibits the activity of $CYP_{450}3A4$, resulting in a slow rate of metabolism in the gut. Consequently, the bioavailability of orally administered drugs will increase due to the inhibition of $CYP_{450}3A4$ in the intestinal lumen, causing a reduction in the first-pass effect. As mentioned earlier, the components of GFJ considered to be responsible for inhibiting the activity of $CYP_{450}3A4$ are furanocoumarins (25). It should be noted that DHB is also able to inhibit other isoenzymes such as $CYP_{450}1A2$. Bergamottin (BG), another component of GFJ, was found to inhibit the actions of a number of isoenzymes,

TABLE 1
Effect of grapefruit juice (GFJ) on the pharmacokinetic parameters of cardiovascular drugs in humans

Drug	Number of subjects	AUC (ng·h/mL) Control	AUC (ng·h/mL) GFJ	C_{max} (ng/mL) Control	C_{max} (ng/mL) GFJ	t_{max} (h) Control	t_{max} (h) GFJ	$t_{½}$ (h) Control	$t_{½}$ (h) GFJ	Reference
Verapamil	9 males	215±102	292±146*	26±13	41±25	3.9±1.0	4.6±1.0	10.1± 4.0	8.3 ±2.0	43
	6 males 6 females	533±257	763±315	63.5±34.9	101.5±46.2	N/A	N/A	4.3±2.0	4.3±1.6	44
Diltiazem	9 males	812±302	890±235	140±42	143±58	2.6±0.7	2.7±0.6	4.1±1.2	5.1±0.7*	45
Nisoldipine	5 males 3 females	78.1±11	321±46*	24.0±3.4	118±19*,[b]	1.50±0.16	1.69±0.33	1.86±0.33	1.42±0.11	49
Nimodipine	8 males	76.0	115.0*	34.0	42.0d	0.8	1.7	9.5	8.3	51
(+)-Nicardipine	6 males	355.2±57.5	509.7±170.2*	N/A	N/A	N/A	N/A	N/A	N/A	52
Amlodipine	12 males	94	107*	2.7	3.1*,[j]	7.0	7.6	35.8	35.8	54
Pranidine	16 males	18.41	31.89*	3.26	4.98*	2.63	3.00	7.65	7.32	53
Losartan	7 males 2 females	523±200	611±169	265±100	270±113	1.5 ±0.7	2.2±2.8	1.9±0.8	1.7±0.7	61
Simvastatin	9 males 1 female	27.8±13.7	373±118*	9.3±4.5	112±22.8*	2.0	4.0*	2.7±0.5	2.5±0.6	57
Lovastatin	16 males	23±10	55±16*	4.3±4.3	9.7±7.1*	3.1±1.8	2.1±0.8	3.5	3.3	59
Atorvastatin	6 males 6 females	58.1±34.7	143.2±82.7	12.7±7.8	13.4±7.3	1.0	3.0*	7.8±3.6	13.3±6.2*	60
Digoxin	7 males 5 females	13.87±2.49	15.2±3.0*,[a]	2.2±0.4	2.7±0.9	1.3	1.2	N/A	N/A	62
Quinidine	12 subjects	27.3±8.7	29.6±12.0	3.0±1.1	2.8±1.1	1.6±0.5	3.3±1.0*	11.2±4.6	12.4±4.9	64
	6 males	2.0	2.1h	N/A	N/A	N/A	N/A	7.0	8.3*	65
Amiodarone	11 males	23.9±11.2	35.9 ±14.3*,[l]	1.87±0.6	3.45±1.7*,[f]	4.08±1.66	3.63±0.96	11.56±8.0	9.53±5.5	67

**P<0.05 treatment versus control (water). [a]Data obtained 24 h after ingestion of GFJ and interactive drug; units reported by the authors: [b]×10^{-6}% of dose; [c]×10^{-6}% of dose·h/mL; [d]body weight (g)/mL; [e]body weight (g)·h/mL; [f]µg/mL; [g]mg·h/mL; [h]µM; [i]µg·h/mL; [j]ng/L. AUC Area under the plasma time curve; C_{max} Maximal plasma concentration; N/A Data not available; $t_{½}$ Plasma half-life of parent drug; t_{max} Time to reach maximal plasma concentration*

namely 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4. It was also found that BG had to be metabolized before the enzyme inhibition occurred (26). Metabolites of either DHB or BG have been hypothesized to participate in a mechanism-based inhibition whereby they bind to CYP_{450}3A4 active sites (22,27), and the degree of inhibition is concentration and time dependent (28). Like GFJ, red wine contains compounds that exhibits a similar inhibition mechanism because its interactive action is concentration, time and NADPH dependent (29).

Recent work has suggested that the inhibitory action of GFJ is due to the downregulation of CYP_{450}3A4 enzymes. Lown and colleagues (30) found that repeated ingestion of GFJ caused a reduction in the amount of enterocyte CYP_{450}3A4 isoenzymes in all human subjects enrolled in their study. The reduction in intestinal concentrations of CYP_{450}3A4 enzymes was localized to this tissue because no significant decreases were observed in colonic and hepatic tissue (30).

Inhibition of P-gp transporters by GFJ

When it was discovered that certain cancers were becoming resistant to chemotherapy, such multidrug resistance was linked to an efflux pump in cancer cells, and this pump was identified as belonging to the family of ATP binding cassette transporters. This pump was named P-gp (23,24,27). P-gp transporters are expressed at several sites within the body: the brush border of proximal renal tubule epithelium, the luminal surface of biliary hepatocytes, the mucosa of small and large intestine, and in pancreatic ductules (27). Commonly used medications have been identified as activators or inhibitors of P-gp transporters, and some drugs, such as cyclosporine, verapamil, and diltiazem, have both activating and inhibitory effects (27). When P-gp is activated, it causes a reduction in serum levels of a drug due to the efflux action of P-gp. Of the previously mentioned active components of GFJ, either BG or DHB was found to be responsible for inhibiting P-gp (25,31). The inhibitory effect of GFJ on P-gp has been observed in in vitro studies involving Caco-2 monolayer cells, which have P-gp expressed on them. Caco-2 cells are derived from colonic adenocarcinoma tissue. The addition of GFJ was able to cause a significant difference in the absorption of racemate talinolol that was transported from the apical to basolateral sides of the Caco-2 monolayer cells (32).

If CYP_{450}3A4 and P-gp were induced simultaneously by a xenobiotic, there would be a reduction in the plasma concentrations of a given drug due to the increased activity of each mechanism, but the extent of effect of P-gp is generally under-recognized because it does not affect drug plasma concentrations with the same magnitude as does the CYP_{450}3A4 system (33).

RECOGNIZED INTERACTIONS OF GFJ AND CARDIOVASCULAR MEDICATIONS

By inhibiting the activity of CYP_{450}3A4 and/or P-gp, GFJ would markedly alter the bioavailability and serum levels of an interacting drug. The resulting high blood levels of a therapeutic agent may have profound adverse consequences on a patient, especially with drugs with narrow therapeutic margins. GFJ's effects on the pharmacokinetic parameters of different cardiovascular drugs in humans and rats are summarized in Tables 1 and 2.

TABLE 2
Effect of grapefruit juice (GFJ) on the pharmacokinetic parameters of cardiovascular drugs in rats

Drug	Species	AUC (μg·min/mL)		C_{max} (ng/mL)		t_{max} (h)		$t_{½}$ (h)		Reference
		Control	GFJ	Control	GFJ	Control	GFJ	Control	GFJ	
Nifedipine	Wistar-ST	4.85±1.75	7.86±2.29	5.02±1.90[b]	5.98±1.73[b]	0.20±0.05	0.27±0.14	1.31±0.32	1.19±0.27	46
Nifedipine	Sprague-Dawley	345.0[c]	700.0*[,a,c]	5230.0	2097.0*[,a]	23.0[d]	443.0*[,a,d]	31.0[d]	70.0*[,a,d]	47
Talinolol	Sprague-Dawley	19.3	29.9*	77.5	163.6*	204±32.9[d]	170±24.5[d]	N/A	N/A	32

**P<0.05 when compared with treatment versus control (water) group. [a]Rats were treated with concentrated grapefruit juice; Units given in concentrations of: [b]μg/mL; [c]μg·h/mL; [d]min. AUC Area under the plasma time curve; C_{max} Maximal plasma concentration; t_{max} Time to reach maximal plasma concentration; $t_{½}$ Plasma half-life of unmetabolized drug*

TABLE 3
Effect of grapefruit juice (GFJ) on felodipine pharmacokinetics: results from six different studies

Number of subjects studied	AUC (nmol·h/L)		C_{max} (nmol/L)		t_{max} (h)		$t_{½}$ (h)		Reference
	Control	GFJ	Control	GFJ	Control	GFJ	Control	GFJ	
9 males	101.7	145.9*	9.2	17.7*	3.4	2.4	9.0	9.4	42
15 males	35.3±21.6	76.4±15.6*	5.5±3.4	17.9±3.3*	N/A	N/A	N/A	N/A	16
12 males	66.8	115.0*	6.7	18.3*	4.0	2.9	8.6	8.7	41
12 subjects	24.0±5.0	69.0±11.0*	3.0±1.0	12.0±2.0*	N/A	N/A	N/A	N/A	38
10 males, 2 females	25.0±5.0	54.0±8.0*	7.0±1.0	16.0±2.0*	4.5±0.4	3.1±0.2*	2.9±0.6	3.7±0.7*	9
5 males, 5 females	38.6±5.5	74.7±8.8*[,a]	7.4±1.4	13.9±1.7*[,a]	3.4±0.3	3.4±0.4	8.8±1.5	7.7±1.3	7

**P<0.05 when compared with treatment versus control (water) group. [a]Control group used orange juice as opposed to water in other studies. AUC Area under the plasma time curve; C_{max} Maximal plasma concentration; N/A Data not available; $t_{½}$ Half-life of parent drug; t_{max} Time to reach maximal plasma concentration*

It appears that there are no sex-related differences when GFJ and different cardiovascular drugs are taken concomitantly, but further studies are required to monitor any pharmacokinetic or pharmacodynamic differences in males and females. Our literature search showed that most studies were performed on healthy adults and only one study was done on elderly subjects. Due to ethical considerations, all studies were performed on healthy subjects and most studies primarily had male subjects. The use of healthy subjects without any form of cardiovascular disease does not illustrate the effect of the GFJ interaction properly. Further studies must be performed with volunteers diagnosed with cardiovascular disease to elucidate the adverse effects associated with GFJ.

In studies discussed in this review, single- or double-strength GFJ was administered in volumes of either 200 mL or 250 mL together with cardiovascular medications at therapeutic dosages (34,35), except for verapamil, which was administered at three dose levels: 60 mg (low dose), 120 mg (normal dose) and 240 mg (high dose) (36).

Interaction of GFJ with calcium channel blockers

Calcium channel blockers (CCBs) are used for treating hypertension, angina pectoris, arrhythmias, atherosclerosis and nephropathy. There are three classes of these drugs: phenylalkylamines, benzothiazepines and dihydropyridines. Drugs within each class show close structural homology, and this suggests that GFJ consumption should be taken with extreme caution when taken with any CCBs, even if there are no reported interactions with each class of CCBs.

One of the most widely studied dihydropyridines is felodipine with respect to its interactions with GFJ. An in vitro study involving human and rat microsomes showed that the metabolism of (R)-felodipine was faster than (S)-felodipine, but this stereoselectivity was negated by the inhibitory effect of GFJ. The inhibition of dihydropyridines was found to be dependent on the concentration of flavonoids in GFJ (37). Results of six studies done by independent investigators show that concomitant use of GFJ with felodipine causes a marked increase in the area under the curve (AUC) and C_{max} values of this drug, without causing a significant change in the time to reach maximal plasma concentration (t_{max}) (6,38-42). The overall evidence gathered from these studies provides conclusive proof about the possible dangers associated with the combined intake of felodipine and GFJ. The interactions have been observed in all age groups and in both sexes, and the increases in AUC and C_{max} values are always significant. All published reports indicate a marked reduction in diastolic blood pressure and heart rate, which is linked to the interaction of felodipine with GFJ. The effects of GFJ on felodipine pharmacokinetics are shown in Table 3.

In earlier studies, no interaction was found with consumption of verapamil and GFJ because a single ingestion of GFJ did not affect the pharmacokinetics of verapamil (36). Subsequently, in a randomized, crossover study, Ho et al (43) demonstrated in nine healthy male volunteers (aged 19 to 40 years) that concurrent use of GFJ and S-verapamil caused a significant increase in the AUC (from 215±102 ng·h/mL to 292±146 ng·h/mL; P=0.04) and C_{max} (from 26±13 ng/mL to 41±25 ng/mL; P=0.08), and results for R-verapamil were similar in magnitude. No change in the elimination half-life or renal clearance of R- and S-verapamil metabolites was observed. In the two treatment periods, the combination did

not produce significant changes in blood pressure, heart rate or PR-interval (43).

Fuhr et al (44) demonstrated in a randomized, crossover study that the concomitant use of (R,S)-verapamil and GFJ caused a 1.45-fold increase in AUC and a 1.63-fold increase in the C_{max} of verapamil at steady state levels. Their study, performed in 12 adult male and female volunteers (27±4 years old), showed a slight prolongation in the PR-interval, but the difference was considered to be 'borderline significant' by the researchers. In this study, both verapamil and verapamil nonenantiomers were used to investigate the effects of GFJ (44). Both studies conclude that the change in the pharmacodynamics of verapamil is due to the inhibitory action of GFJ on the intestinal $CYP_{450}3A4$ isoenzymes.

When a benzothiapene-type agent, diltiazem, was taken with GFJ, there were no large significant changes in the pharmacokinetics of diltiazem, but there was a significant increase in the plasma half-life of diltiazem (from 4.1±1.2 h to 5.1±0.7 h; $P<0.05$). Measurement of the metabolites showed no changes in the metabolite-to-parent drug ratios, but there were changes in the PR-intervals and mean arterial pressures of the subjects studied (45).

Dihydropyridines constitute the largest group of the CCBs (including amlodipine, felodipene, isradipene, nicardipene, nifedipine, nimlodipine, nisoldipene and nitrendipene). Experiments with rat duodenums showed that BG, a furanocoumarin, causes a significant increase in the AUC of nifedipine. The AUC was 1.5 times larger in the treatment group than in the control group (7.86±2.29 µg·hr/mL versus 4.85±1.75 µg·hr/mL; $P<0.01$). There was also a decrease in the apparent oral clearance from 0.18±0.05 L/h to 0.11±0.03 L/h (46). These results are in agreement with the findings of Grundy et al (47), who had examined the effects of GFJ and orange juice concentrate and found that only GFJ increased the bioavailability of nifedipine. When nifedipine was given intravenously to GFJ pretreated rats, there was no change in the pharmacokinetic values, and only the oral administration of nifedipine to rats caused a profound increase in the AUC (from 345 µg·min/mL to 700 µg·min/mL; $P<0.05$) and a decrease in the renal clearance of nifedipine (from 17.4 mL/min·kg to 8.6 mL/min·kg; $P<0.05$). These results suggest that GFJ only exerts its effects in the small intestine (47).

Mohri et al (48) administered GFJ to rats twice a day for 10 consecutive days, and on the eleventh day, there was a significant increase in the apparent clearance of nifedipine (from 0.21±0.02 nmol/mg/min to 0.32±0.05 nmol/mg/min). The dosing of GFJ to the rats also caused a gradual increase in CYP_{450} content (from 0.045±0.009 nmol/mg to 0.060±0.007 nmol/mg). The results of this study clearly showed that short-term use of GFJ is able to increase the bioavailability of nifedipine due to the inhibition of CYP_{450}, while the long-term use may decrease its bioavailability due to the induction of CYP_{450} in enterocytes (48).

Takanaga et al (49) showed that when nisoldipine was taken concomitantly with GFJ, both the C_{max} (from $24.0\pm3.4\times10^{-6}$% of dose·mL^{-1} to $118\pm19\times10^{-6}$% of dose·mL^{-1}; $P<0.01$) and AUC (from $78.1\pm11\times10^{-6}$% of dose·h·mL^{-1} to $321\pm46\times10^{-6}$% of dose·h·mL^{-1}) increased significantly in eight subjects (22 to 26 years old). The concomitant use of GFJ and nisoldipine had no effect on heart rate, but the combination caused significant decreases in the systolic and diastolic blood pressures of their subjects (49). A recent crossover study performed in Japan in eight healthy, adult male volunteers indicated that both AUC and C_{max} of nifedipine or nisoldipene increased by a factor of approximately 1.5 times when the pulp of a grapefruit (200 g, or roughly one grapefruit) was eaten. This interactive effect is similar to that previously reported with dihydropyridines and GFJ (50).

Fuhr et al (51) conducted a randomized, crossover study in eight adult male volunteers (four smokers and four nonsmokers, 23 to 29 years old), and the combined administration of nimodipine and GFJ caused an increase in C_{max} (from 34 g body weight/L to 42 g body weight/L) and AUC (from 76 g body weight·h/L to 115 g body weight·h/L). There was also a slight reduction in the ratio of AUC metabolite to AUC nimodipine. The use of GFJ with nimodipine also caused an increased hemodynamic response (systolic and diastolic blood pressure and heart rate), but the increases were slight and corrected themselves within 24 h (51).

Dihydropyridines are enantiomeric in nature, and in some cases, the use of a racemic mixture may be more harmful to an individual after GFJ consumption. In a crossover study, Uno et al (52) examined the effect of (+)- and (–)-nicardipine in six male subjects (23 to 29 years old). The results showed that GFJ increased the mean AUC and clearance of both (+)- and (–)-nicardipine, but the increase of these parameters was large with respect to (–)-nicardipine. The AUC of (+)-nicardipine increased from 355.2±57.5 ng·h/mL to 509.7±170.2 ng·h/mL ($P<0.05$), and the mean clearance decreased from 0.99±0.27 L·h/kg to 0.73±0.24 L·h/kg ($P<0.05$). Both (+)- and (–)-nicardipine caused an increase in heart rate, but they had no significant effect on other hemodynamic factors such as diastolic and systolic blood pressure. The large difference in pharmacokinetic parameters between the two enantiomers suggests the potential risk of solely consuming (–)-nicardipine with GFJ (52).

Hashimoto et al (53) studied the effects of GFJ on pranidine in 16 healthy males. An open-label, crossover design resulted in significant increases in the AUC (from 18.41 ng·h/mL to 31.89 ng·h/mL; $P=0.0005$) and C_{max} (from 3.26 ng/mL to 4.98 ng/mL; $P=0.0003$) of pranidine, but there were no significant increases in the t_{max} or the half-life. In the GFJ and control groups, subjects complained of hot flushes, and an elevated heart rate was observed in the subjects throughout the study (53).

An interaction with amlodipine and GFJ was reported by Josefsson et al (54). A single dose of GFJ with amlodipine was able to cause an increase in the AUC (from 94 ng·h/mL to 107 ng·h/mL; $P<0.05$) and C_{max} (from 2.7 ng/L to 3.1 ng/L; $P<0.05$) in 12 healthy subjects (21 to 38 years old), but no change in t_{max} was observed. In the GFJ-treated group, there was a significant decrease in blood pressure ($P<0.01$), but basal levels in blood pressure returned 12 h after dosing (54). In a randomized, open-label, placebo-controlled, four-way crossover study involving amlodipine and GFJ, Vincent et al (55) did not find any significant changes in the pharmacokinetics or pharmacodynamics of amlodipine in 20 healthy male subjects (aged 20 to 45 years) (55). Despite the negative results of this study, concurrent use of GFJ with amlodipine should be avoided, considering the findings of previous studies as well as the structural homology of amlodipine with other dihydropyridines.

Lercanidipine is a new dihydropyridine CCB, and there are currently no studies available that describe an interaction

with GFJ. However, there is potential of an interaction because it is a known $CYP_{450}3A4$ substrate and other $CYP_{450}3A4$ inhibitors such as ketoconazole have been shown to interact with lercanidipine (56). Consumption of this CCB with GFJ should be used with extreme caution or avoided completely.

Dresser et al (38) investigated the effect of concomitant use of GFJ and felodipine in 12 healthy elderly individuals (70 to 83 years old). The AUC and C_{max} values were 2.9-fold and 4.0-fold greater, respectively, when compared with control values. The AUC increased from 24±5 nmol·h/L to 69±11 nmol·h/L, while the C_{max} increased from 3±1 nmol/L to 12±2 nmol/L. Four hours after the ingestion of the GFJ-felodipine combination, there were significant reductions in the systolic (–13±3 mmHg; P<0.01) and diastolic (–7±1 mmHg; P<0.001) blood pressures. Two and three hours after the GFJ-felodipine ingestion, the heart rates of 12 participants were higher (+3±1 beats/min; P<0.01). Results of this study show that concomitant use of GFJ and felopdipine by elderly patients should be avoided due to their susceptibility to hypotension-related adverse events (38). The data from this study confirm the pharmacokinetic trends seen in similar studies done with felodipine (Table 3).

Information is presently lacking for the combined effects of GFJ and CCBs in pregnant and nursing women, as well as in children. Further studies are warranted in these groups. However, in view of the studies reported above, the use of GFJ and CCBs in these groups should also be avoided.

Interaction of GFJ with lipid-lowering agents

Among the four classes of lipid-lowering agents currently marketed in Canada, only the HMG-CoA reductase inhibitors, also known as statins, have been found to interact with GFJ. In a nonrandomized, crossover study, Lilja et al (57) found that consumption of simvastatin and GFJ in 10 healthy subjects (20 to 34 years old) had similar effects as observed with CCBs because there were significant increases in simvastatin's AUC (from 27.8±13.7 ng·h/mL to 373±118 ng·h/mL; P<0.001) and C_{max} (from 9.3±4.5 ng/mL to 112±22.8 ng/mL; P<0.001). A marked increase in t_{max} was also observed (from 2 h to 4 h; P<0.05) (57).

Rogers et al (58) conducted a randomized, crossover study and found that both the AUC and the C_{max} of lovastatin increased when this drug was taken with GFJ. The C_{max} (from 4.3±4.3 to 9.7±7.1 ng/mL; P<0.05) and the AUC (from 23±10 ng·h/mL to 55±16 ng·h/mL; P<0.05) increased significantly in their 16 healthy male subjects (18 to 39 years old) (58). Kantola et al (59) also observed a similar interaction when they investigated the effect of GFJ on lovastatin pharmacokinetics. The AUC of lovastatin increased 15-fold (P<0.001) and the C_{max} increased 12-fold (P<0.001). Lovastatin's metabolite, lovastatin acid, also exhibited similar increases with respect to AUC and C_{max}, but they did not increase by the same magnitude (59).

Lilja et al (60) investigated GFJ's effects on atorvastatin in 12 subjects (19 to 27 years old) and pravastatin in 11 subjects (21 to 31 years old) in two randomized, two-phased, crossover studies. Atorvastatin produced similar interactive effects as other HMG-CoA reductase inhibitors when taken with GFJ, but pravastatin did not show any increase in either AUC or C_{max}. The atorvastatin AUC increased from 58.1±34.7 ng·h/mL to 143.2±82.7 ng·h/mL (P<0.01), while there was no significant change in the C_{max}. There were significant increases in the t_{max} (from 1 h to 3 h; P<0.01) and elimination half-life (from 7.8±3.6 h to 13.3±6.2 h; P<0.01) of atorvastatin. Pravastatin showed only a prolongation in the t_{max} of active HMG-CoA reductase inhibitors (from 1 h to 2 h; P<0.05) (60). Simultaneous administration of pravastatin with GFJ should still be done with caution because of its structural similarities to other statins.

Although no interactions with fibrates (eg, benzafibrate, clofibrate, fenofibrate and gemfibrozil) and GFJ have been reported, caution should be exercised in the co-administration because fibrates are known substrates of $CYP_{450}3A4$. It is not known whether fibrates undergo a high degree of first-pass metabolism, and further studies are warranted to verify this phenomenon.

Interactions of GFJ with angiotensin II receptor antagonists

Angiotensin II (A-II) receptor antagonists (eg, candesartan cilexetil, eprosartan mesylate, irbesarta, lostartan potassium, telmisartan and valsartan) block A-II from binding to its receptors. A-II is a potent vasoconstrictor and increases blood pressure. The inhibition of A-II receptors allows vessels to dilate, resulting in lowering blood pressure.

At the present time, there are six A-II receptor antagonists marketed in Canada: candesartan cilexetil, eprosartan mesylate, irbesartan, losartan potassium, telmisartan and valsartan. Of these six agents, there is only one report of an interaction between losartan and GFJ. A randomized, crossover study showed that the AUC of losartan increased insignificantly in nine subjects (32 to 46 years old), and the time to drug appearance in serum was prolonged (from 0.6±0.5 h to 1.3±0.5 h; P<0.04). GFJ also caused a change in the pharmacokinetic properties of the pharmacologically active metabolite (E3174) of losartan. The half-life of the metabolite as well as the mean retention time were significantly increased; however, the AUC was decreased (P<0.0371). Losartan is thought to be primarily metabolized by $CYP_{450}2C9$, but the results of this study show that GFJ's effect on $CYP_{450}3A4$ in the gut is able to alter the pharmacokinetics of losartan (61). Further experiments are needed to validate the interactive effect between GFJ and losartan.

Interaction of GFJ with beta-adrenergic blockers

Beta-adrenergic blockers are useful for the treatment of angina and hypertension. They produce their pharmacological action by specifically blocking beta-1 adrenergic receptors. Spahn-Langguth and Langguth (32) used talinolol, a P-gp substrate, in both in vivo and in vitro studies. The in vitro studies involved a monolayer of Caco-2 cells, wherein the apical-to-basolateral transport increased over 3-fold in the presence of GFJ (from 0.16×10^{-6} to 0.61×10^{-6} cm/s). Their study in rats showed that concomitant administration of talinolol and GFJ caused significant increases in the C_{max} (from 77.5 ng/mL to 163.6 ng/mL; P<0.05) and AUC (from 19.3 µg·min/mL to 29.9 µg·min/mL; P<0.05), and a decrease in renal clearance (from 382±128 mL/min to 182±85.6 mL/min) of this drug (32). If talinolol is given to patients using GFJ, the dose of talinolol needs to be adjusted to prevent a large drop in blood pressure.

While there have been no reported cases of interaction between GFJ and other beta-1 adrenergic blockers, concomitant use of these drugs with GFJ should be avoided in view of the in vitro and in vivo evidence.

Interaction of GFJ with antiarrhythmic drugs

There is a variety of drugs available for the treatment of arrhythmias such as cardiac glycosides, beta-adrenergic blocking agents, CCBs and quinidine. The calcium channel blocking agents used for treating arrhythmias are verapamil and diltiazem, and their interactions were mentioned previously.

Digoxin is the commonly used cardiac glycoside, but unfortunately it has a narrow therapeutic index, and high plasma concentrations (>1.5 ng/mL, or 1.3 nM) of this drug are associated with acute cardiotoxicity (62,63). Becquemont et al (64) conducted an open randomized study that investigated the interaction of GFJ with digoxin in 12 subjects (aged 19 to 35 years). They found that when digoxin is taken concomitantly with GFJ, there is no marked increase in C_{max}, but there is a significant increase in the AUC during the first 4 h (from 5.39±0.81 ng·h/mL to 6.0±1.2 ng·h/mL; P=0.01), as well as at 24 h (from 13.87±2.49 ng·h/mL to 15.2±3.0 ng·h/mL; P=0.01) (64). These results suggest that if a subsequent dose of digoxin is taken during the first 24 h after GFJ ingestion, dangerous plasma levels of this cardiac glycoside might be reached and cause electrical and mechanical disturbances in the heart.

Investigation of interactions of GFJ with quinidine was prompted by an early in vitro study showing that flavonoids from GFJ inihibited the metabolism of quinidine and midazolam (65). When quinidine was taken with GFJ during a randomized, crossover trial, there were no changes in the AUC or C_{max} in 12 adult male subjects (aged 19 to 27 years), but there was a significant increase in the t_{max} (from 1.6±0.5 h to 3.3±1.0 h; P=0.001). A reduction in the AUC of quinidine's metabolite, 3-hydroxyquinidine, was also noted (from 5.7±3.6 mg·h/L to 4.3±3.1 mg·h/L; P=0.01). As expected, the time delay to reach its maximal concentration caused a reduction in quinidine's pharmacodynamic parameters because there was a delay in the time required to correct the QT-interval in the experimental subjects. There was a decrease in heart rate (from 5 beats/min to 8 beats/min) and mean blood pressure in all participants, but these parameters returned to normal after 4 h to 6 h (66). In another study, Damkier et al (67) performed an open study in six males (aged 20 to 35 years) and showed that concomitant use of quinidine and GFJ caused a reduction in the total clearance of quinidine (~15%), partial clearance of quinidine by 3-hydroxylation (~19%) and N-oxidation of quinidine (~27%). It prolonged the elimination half-life of quinidine (from 7.0 h to 8.3 h) (67).

Libersa et al (68) observed that GFJ completely inhibited the production of amiodarone's metabolite, N-desemethylamiodarone, in all 11 participants (aged 19 to 40 years) in their single-sequence, repeated-measures design study. GFJ also significantly increased the AUC (from 23.9±11.2 µg·h/mL to 35.9±14.3 µg·h/mL; P<0.005) and the C_{max} (from 1.87±0.6 µg/mL to 3.45±1.7 µg/mL; P<0.02) of amiodarone. The reduction in serum levels of amiodarone metabolite was proportional to the decrease in effectiveness of amiodarone in altering PR- and QT-intervals (68).

Interaction of GFJ with sildenafil citrate

Sildenafil citrate, specific inhibitor of phosphodiesterase-5, is used for the treatment of male erectile dysfunction. When administered orally, sildenafil undergoes extensive first-pass metabolism and only 40% of the active drug reaches the systemic circulation. The metabolism of sildenafil is mediated by two hepatic cytochrome P-450 isoforms: $CYP_{450}3A4$ (major route) and $CYP_{450}2C9$ (minor route). In a randomized, crossover study, Jetter et al (69) showed that simultaneous administration of sildenafil and GFJ caused a 23% increase in the AUC and a 15 min increase in t_{max}. Insignificant changes in systolic and diastolic blood pressures and heart rate occurred in 24 male subjects (aged 29±5.1 years) (69). Another study found that concomitant use of GFJ and sildenafil markedly increased the C_{max} of sildenafil from 1067.7 ng/mL to 1517.0 ng/mL in a single elderly subject (70). Additional studies in elderly patients are warranted to clearly establish the GFJ-sildenafil interaction to properly evaluate the health risks associated with the interaction.

GFJ-induced inhibition of $CYP_{450}3A4$ in enterocytes may give rise to high plasma levels of sildenafil. The potentially deleterious interactions between sildenafil and GFJ may even become more pronounced in patients taking the largest recommended dose (100 mg) of this drug and in patients who already have compromised kidney and/or liver functions.

Interaction of GFJ with warfarin

Warfarin is another drug with a narrow therapeutic index, and its R and S enantiomers have differing potencies. (S)-warfarin is three to six times more potent than (R)-warfarin, and it is metabolized via $CYP_{450}2C9$, while (R)-warfarin is metabolized via $CYP_{450}1A2$ and $CYP_{450}3A4$. In an open-label study, Sullivan et al (71) studied the interaction of previously frozen GFJ and warfarin in 10 healthy men (aged 55 to 75 years) with an international normalized ratio between two and three. Only nine males completed the study, and there were no significant differences in the international normalized ratio and prothrombin times in the nine males after GFJ ingestion (71). Further studies are needed to confirm or refute the findings of this warfarin-GFJ interaction report.

CONCLUSIONS

In view of the potential interactions observed between GFJ and cardiovascular medications, physicians should give due consideration to the adjustment of dosages of interacting drugs or advise patients to remove GFJ from their diet. The risk will vary depending on which class of cardiovascular drug is being used. Drugs having narrow therapeutic margins should be carefully scrutinized to prevent any serious adverse events. While not all drugs belonging to a particular class of medications are mentioned in the present review, great caution should be exercised with any drug having a narrow therapeutic index, as well as CCBs with low bioavailability (eg, felodipine, nisoldipine), when taken concomitantly with GFJ.

On June 21, 2002, Health Canada issued a Public Advisory about the possible serious adverse effects observed after the combined administration of GFJ and a wide variety of drugs (72). In December 2002, the Australian drug regulatory authority issued a similar warning of drug-GFJ interaction in the *Australian Adverse Drug Reaction Bulletin* (73). Information about the health risks and patient management options as well as the pharmacokinetic and pharmacodynamic effects observed in healthy volunteers following the combined administration of GFJ and several pharmacologically unrelated drugs also appear in the latest edition of the Canadian *Compendium of Pharmaceuticals and Specialities* (74). The author, however, adds a caveat: "It should not be assumed that the drugs in the table should never be taken concomitantly with grapefruit juice or that drugs not appearing in the table do not interact."

Most clinical studies have involved a single use or short-term exposure to GFJ and the test drugs, while the effects of long-term combination remain unknown. To properly assess the potential toxicity risks of GFJ and cardiovascular medications, additional investigations should be conducted in patients or suitable animal models after the multiple or long-term use of GFJ. Such studies would reveal if alterations observed in the pharmacokinetic/pharmacodynamic parameters of interacting drugs after short-term exposure to GFJ revert to control levels following multiple exposures to GFJ. It is also possible that long-term use of GFJ may cause induction or enhance the activities of $CYP_{450}3A4$ and P-gp, as well as some other drug-metabolizing enzymes in the liver and gastrointestinal tract, and subsequently cause reduction in therapeutic plasma levels of certain drugs. Further studies are warranted in appropriate in vivo and in vitro models to identify the GFJ constituents responsible for the inhibitory activities of $CYP_{450}3A4$ and P-gp and to understand the underlying mechanisms of GFJ-drug interactions.

Collaborative efforts are required from patients, physicians, pharmacists and the industry (drug manufacturers) to minimize or possibly prevent any potential risks associated with GFJ and interacting drugs. Due consideration should be given to proper labelling of drug product monographs to ensure that patients, physicians and pharmacists are aware of the possibility of specific GFJ-drug interactions. Before prescribing a medication, physicians may inquire as to whether their patients are consuming GFJ and either instruct their patients to stop consuming GFJ or adjust drug dosages to compensate for GFJ effects.

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