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Drug Interactions with Grapefruit Juice: An Evidence-Based Overview

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Behavioral Objectives

After completing this continuing education article, the pharmacist should be able to:

1. Identify the mechanism of grapefruit juice-drug interactions and drugs involved with significant grapefruit-drug interactions
2. Describe potential effects of grapefruit juice-drug interactions.
3. Discuss medications that may be affected and degree of risk associated with common interacting medications.
4. Identify effective alternative medications that do not interact (for patients who do not want to comply with dietary restrictions).
5. Articulate the public health implications of media myths and inaccurate information surrounding this issue.
6. Describe the pharmacist's role in communication the food-drug interaction issue to patients and physicians.
7. Effectively explain drug interaction risk factors and effective, alternative medications for patients.

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Table 2. Potential Interactions Between Grapefruit Juice and CYP3A4 Substrates

Drug Class	Drugs(s) with Significant Grapefruit Juice Interaction	Drug(s) with Negligible Grapefruit Juice Interaction	Findings with Significant Interaction	Implications with Significant Interaction
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Anti-arrhythmics	Amiodarone		Increases AUC by 50% and peak plasma concentration by 84%. Both PR and QRS intervals were not significantly altered and systolic arterial pressure decreased slightly. ⁴²	Watch for arrhythmias and toxicity.
	Quinidine		Delays absorption of quinidine and inhibits the metabolism of active metabolite. ⁴³	Clinical significance is unknown.
Anti-convulsant	Carbamazepine		Increases AUC, peak and trough concentrations by 40%. ⁴⁴	Watch for signs of toxicity such as dizziness, ataxia, drowsiness, nausea, vomiting, tremor, and agitation. Monitor blood levels.
Anti-depressant	Sertraline Trazodone Nefazodone Clomipramine		Increases plasma concentrations.	Watch for increases in side effects.
Anti-histamine	Fexofenadine	Desloratadine	May decrease oral absorption and blood levels by inhibiting the organic anion transporting polypeptide. ²⁴	Clinical significance is unknown.
Anti-	Carvedilol		Increases bio-	Clinical significance

hypertensive	Losartan		availability of a single dose by 16%.	is unknown
			May reduce the AUC of the major active metabolite.	May reduce effectiveness of losartan but further studies are needed to determine significance.
Anxiolytics & hypnotics	Diazepam Midazolam Triazolam Buspirone	Alprazolam	Increased plasma concentrations.	Watch for possible increase in sedation.
Caffeine			Decreases caffeine clearance. ^{45,46}	Watch for possible increase in side effects such as nervousness or insomnia.
Calcium channel blockers	Felodipine Nicardipine Nifedipine Nimodipine Isradipine Verapamil	Amlodipine Diltiazem	Increased plasma concentrations. ⁴⁷	Watch for toxicity, such as flushing, headache, tachycardia, and hypotension.
Cortico-steroids	Methylprednisolone, oral	Prednisone	Increased plasma concentrations.	Consumption of large amounts of grapefruit juice may increase the risk of adverse effects.
	Budesonide		Increases oral absorption. ¹	Watch for hypercorticism.
Estrogens	Ethinyl estradiol		Increased plasma concentration.	Clinical significance is unknown.
HMG-CoA reductase inhibitors	Atorvastatin Lovastatin Simvastatin	Fluvastatin Pravastatin	Increased plasma concentrations.	Increased toxicity such as GI complaints and muscle pain.
Immune modulators	Cyclosporine		Increased plasma concentrations of	Watch for signs of toxicity such as

(immuno-suppressants)			cyclosporine. ⁴⁸	hepatotoxicity, renal toxicity, and increased immunosuppression.
	Tacrolimus		Possible increases in plasma concentrations.	Watch for signs of toxicity such as nephrotoxicity, and increased immunosuppression.
Macrolide antibiotics		Erythromycin	Increased plasma concentration.	Clinical significance is unknown.
Protease inhibitors	Ritonavir Nelfinavir Saquinavir	Indinavir Amprenavir	Increases plasma concentrations.	Watch for possible increased side effects.
Others	Sildenafil		Increased bioavailability. ⁴⁹	

AUC = area under the curve; PR = pulse rate; GI = gastrointestinal.

A grapefruit-drug interaction was discovered accidentally in 1989.¹ In a double-blind, placebo-controlled study designed to assess the interaction of ethanol and the dihydropyridine calcium channel blocker, felodipine, the investigators used grapefruit juice to mask the taste of ethanol. Results suggested that the grapefruit juice in the vehicle may have resulted in elevated plasma concentrations of felodipine. A follow-up study confirmed that grapefruit juice increased the systemic bioavailability and augmented the hypotensive effects of the calcium channel blockers felodipine and nifedipine.² Subsequently, studies have demonstrated significant interactions between grapefruit juice and certain drugs (Table).

The grapefruit (*Citrus paradisi*) grows in clusters (like grapes) on a tree. Grapefruit were initially discovered growing in the West Indies in the 1800s, and then brought to the United States where they are currently grown mainly in Florida, California, and Texas. Grapefruit are believed to have evolved from the pummelo, a citrus fruit from the Rutaceae family (orange family), through mutation or as a hybrid with the common orange. The grapefruit is larger than an orange but smaller than most pummelos and can yield approximately 2/3 cup of juice. There are 2 major types of grapefruit: white and pink/ruby red.

As a widely available fruit source to help meet daily nutritional requirements, grapefruit and grapefruit juice are consumed by many individuals for the fiber, vitamin C, antioxidants, and phytochemicals. For this reason, pharmacists need to understand grapefruit/drug interactions as well as common public misinformation, and communicate

any potential interaction risks to patients.

In the past decade, studies have shown that grapefruit juice can induce a several-fold increase in levels of particular drugs that can result in augmented therapeutic or toxic effects. The magnitude and the mechanism of this interaction appear to be the result of a significant inhibition of gut wall cytochrome P-450 3A4 (CYP3A4) isoenzymes and P-glycoprotein (P-gp). This food-drug interaction is of clinical importance because grapefruit or grapefruit juice is consumed by approximately 21% of households in the United States,³ although grapefruit juice consumption in 2001-2002 declined 16% from the previous year. Are consumers being misled to avoid all grapefruit products for fear of potential adverse interactions with all medications? The purpose of this article is to examine the cause of this food-drug interaction; clarify the list of affected medications; and specify the pharmacist's role in counseling patients on options to avoid the possibility of a grapefruit-drug interaction.

Mechanism of Action

Furanocoumarins have been demonstrated to inhibit the first-pass metabolism of certain drugs that are metabolized by CYP3A4. These compounds are found predominantly in the grapefruit flesh followed by the sac, peel, and seed.⁴ The main mechanism of the grapefruit-drug interaction (Figure) appears to result from inhibition of CYP3A4 in the gut wall, and it is most important for drugs with low oral bioavailability (ie, drugs with high first-pass metabolism).⁵ The onset of the interaction can occur within 30 minutes following intake of a single glass of grapefruit juice, and the inhibition can last up to 3 days following the last administration of grapefruit juice.⁶ The magnitude of inhibition of CYP isoenzymes by grapefruit components appears to be greatest for CYP3A4 and less significant for other CYP isoforms (eg, 1A2, 2C9, and 2C19).⁷ Additionally, the interaction appears to affect CYP3A4 in the gut wall to a much greater extent than in the liver.⁵

Originally, naringin was thought to be the main component responsible for grapefruit-drug interactions. However, studies have shown naringin to be a weak inhibitor of CYP3A4.^{8,9} It was also demonstrated that the administration of isolated naringin to humans, in quantities comparable to those found in grapefruit juice, did not cause the same degree of inhibition as grapefruit juice.

In addition to flavonoids, researchers have also focused on furanocoumarins found in grapefruit juice as CYP3A4 inhibitors.^{10,11} Furanocoumarins in grapefruit juice exhibit a mechanism-based inhibition in which a reactive metabolite is formed and covalently binds to the CYP3A4 isoenzyme, resulting in inhibition. The furanocoumarins are divided into 6 components: 6',7'-dihydroxybergamottin (DHB), GF-I-1, bergamottin (GF-I-2), GF-I-4, GF-I-

5 (bergamottin-6',7'-epoxide), and GFI- 6.¹² Significant inhibition of CYP3A4 isoenzyme activity is exhibited by DHB, GF-I-1, and GF-I-4 with minimal activity exhibited by bergamottin (a presumed precursor of GF-I-1 and GF-I-4 and a known ingredient of grapefruit essential oil).¹³ Orange juice has no CYP3A4-inhibiting effects. When orange juice was spiked with a synthetic DHB, however, no significant differences between the degree of inhibition produced by either of the 2 citrus fruits was observed. Therefore, the DHB component in grapefruit appears to be another potent inhibitor of CYP3A4 and is most likely primarily responsible for the interaction.

To thoroughly assess the clinical significance of grapefruit-drug interactions, the type and amount of grapefruit juice must be considered. Consumption of a single 8-oz glass of regular-strength grapefruit juice is sufficient to inhibit CYP3A4. The magnitude of interaction may vary depending on the extent of intestinal CYP3A4 expression in an individual patient. This variation between individuals may be significant and is difficult to predict. The grapefruit-drug interaction appears to affect patients with high quantities of small bowel CYP3A4 isoenzymes.¹⁴

Based on evidence from in vitro, in vivo, and clinical studies, it is now recognized that most drugs do not interact with grapefruit juice. Grapefruitdrug interactions appear to occur only under well-defined circumstances. First, the drug substrate must be predominantly metabolized by CYP3A4. Second, the drug substrate must undergo extensive first-pass metabolism (ie, drugs with low oral bioavailability). Knowledge of these 2 factors will allow pharmacists to predict whether a medication is likely to interact with grapefruit juice. For example, felodipine has a low oral bioavailability of 15% and is significantly affected by grapefruit juice; whereas amlodipine has a high oral bioavailability of 75% and does not interact with grapefruit juice.¹⁵ Other examples are verapamil and quinine. Grapefruit juice significantly increased plasma concentrations of verapamil (oral bioavailability of 20%) and had no significant effect on the pharmacokinetics of quinine (oral bioavailability of 80%).^{16,17}

The CYP3A4 isoenzyme, which is found in the intestine and liver, accounts for about 40% to 60% of all CYP450 isoenzymes (although it is important to note that grapefruit inhibits CYP450 in the gastrointestinal tract, not the liver) and is involved in the majority of significant CYP450-mediated drug interactions. Inhibition of the CYP3A4 isoenzyme, either reversible or irreversible, will result in a reduced metabolism and metabolic clearance of CYP3A4 substrates.

Inhibition of the CYP system occurs through 2 mechanisms. The first and most common mechanism is known as competitive inhibition and results from the competition between the inhibitor and substrate for the same CYP isoenzyme required for substrate metabolism and elimination. The effects of competitive inhibition can be observed after

administration of the first dose of the inhibitor.

The second mechanism is known as mechanism-based inhibition and occurs with grapefruit juice. The most potent grapefruit components causing a mechanism-based inactivation of CYP3A4 are furanocoumarins, which bind irreversibly to CYP3A4 and permanently inactivate the isoenzyme.¹⁸ The duration of mechanism-based inhibition may be longer than competitive inhibition because new CYP3A4 isoenzymes must be synthesized for activity to be restored. Complete recovery of the CYP3A4 may take 48 to 72 hours after the last exposure to grapefruit juice,¹⁹ which explains why the effects can last for at least 72 hours after drinking grapefruit juice.²⁰ Most important, because of mechanism-based inhibition, separating the administration of grapefruit juice and substrate drug by a few hours does not minimize grapefruit-drug interactions. Pharmacists should advise patients to avoid grapefruit entirely if they are taking medications known to significantly interact with grapefruit juice.

In addition to the effect on CYP3A4, grapefruit juice may also inhibit the drug transporters P-gp and organic anion transporting peptide (OATP). P-gp is an efflux membrane transporter pump belonging to the adenosine triphosphate-binding cassette family of proteins.²¹⁻²³ As with CYP3A4, P-gp is found in high concentrations within intestinal enterocytes, the primary site of oral drug absorption. The role of P-gp is to actively secrete absorbed drugs back into the intestinal lumen. After uptake by the enterocyte, the drugs are either metabolized by CYP3A4 or pumped back out (effluxed) into the lumen by the P-gp transporter. Therefore, inhibition of CYP3A4 or P-gp will increase blood levels of the drug substrate. The OATP is a transmembrane sodium- and ATP-independent transporter present in the intestinal mucosa and promotes influx (uptake) of drugs into the enterocytes. Some evidence suggests that active grapefruit components may inhibit intestinal P-gp.²⁴ Preliminary evidence also suggests that grapefruit components inhibit OATP.²⁵ Pharmacists should be aware that grapefruit juice inhibition of OATP results in reduced blood levels of the drug substrate. This is in contrast to inhibition of CYP3A4 or P-gp, which will result in increased levels of the drug substrate. The effect of grapefruit components on P-gp and OATP are still under unclear, however, and additional research is needed.

Grapefruit-Drug Interactions: Increased Blood Levels

Benzodiazepines

Many benzodiazepines, including midazolam and triazolam, are substrates of CYP3A4 and are metabolized by hepatic and intestinal CYP3A4. Coadministration with grapefruit juice did not alter the pharmacokinetics and pharmacodynamics of intravenous

midazolam. After an oral dose of midazolam, however, grapefruit juice significantly increased the peak plasma concentration by 56% and the area under the curve (AUC) by 52%.²⁶ These changes were associated with significant alterations in the pharmacodynamic effects of midazolam, such as delay of the reaction time. Additionally, grapefruit juice increased the AUC (by 50%) and the peak plasma concentration (by 30%) of triazolam in healthy volunteers and was associated with increased drowsiness.²⁷ Caution must be taken when giving oral midazolam, particularly in patients with other causes for increases in midazolam bioavailability, such as advanced age, liver cirrhosis, and coadministration of other CYP3A4 inhibitors. All of these conditions may potentiate the effects of grapefruit juice.

Certain Immunosuppressants

Cyclosporine is an immunosuppressant used widely in solid organ and bone marrow transplantation as well as in the treatment of psoriasis. Oral cyclosporine formulations (ie, oil/water and microemulsion) have been well documented to interact with grapefruit juice through inhibition of CYP3A4 and P-gp. However, intravenous cyclosporine formulations do not interact. In one study, the mean absolute oral bioavailability of cyclosporine increased by 62% with grapefruit juice administration, but there was no significant effect with intravenous cyclosporine.²⁸ The magnitude of pharmacokinetic changes associated with the grapefruit-cyclosporine interaction is variable and unpredictable within individuals and should not be used as a strategy to reduce cyclosporine dosages and save on drug costs.

Tacrolimus is an immunosuppressant metabolized by CYP3A4. Because the bioavailability of tacrolimus is doubled by ketoconazole, a potent CYP3A4 inhibitor, an interaction with grapefruit juice may also occur. Until more data are available, concurrent administration of tacrolimus and grapefruit juice should be avoided.²⁹

Certain Calcium Channel Blockers

The dihydropyridine calcium channel blockers, felodipine, nifedipine, nisoldipine, and nitrendipine, are substrates of CYP3A4 and undergo extensive first-pass metabolism by hepatic and intestinal CYP3A4.^{30,31} When grapefruit juice is administered in combination with oral felodipine, concentrations of felodipine increase significantly compared with felodipine alone.³² When felodipine was administered intravenously with oral grapefruit juice, the plasma concentration of felodipine was not significantly altered. Clinical data show that the ingestion of 1 glass of grapefruit juice can alter felodipine pharmacokinetics for up to 3 days.³³ Thus, when dosing a patient who has been on grapefruit juice, a 3-

day washout period should occur before initiating felodipine.

Verapamil, a nondihydropyridine calcium channel blocker, is commonly used for the treatment of cardiovascular conditions and migraines. In healthy volunteers, administration of verapamil 120 mg twice daily for 3 days plus grapefruit juice 200 mL twice daily for 5 days resulted in a moderate but statistically significant increase in verapamil concentrations. In this study group of healthy volunteers, changes in heart rate or blood pressure were not statistically significant. Clinical effects in more fragile patients may be more significant, however, and the combination of grapefruit juice and verapamil should be avoided.³⁴


HMG-CoA Reductase Inhibitors (Statins)

A study showed that 2 days of pretreatment with 200 mL doublestrength grapefruit juice 3 times a day, as compared with water, prior to administration of lovastatin 80 mg increased the peak concentrations of lovastatin and the metabolite, lovastatin acid, by 12- and 4-fold, respectively.³⁵ The AUC for lovastatin and the metabolite also increased significantly, 15- and 5-fold, respectively. The half-life remained unchanged. In another study, 8 oz (240 mL) of regular- strength grapefruit juice was administered in the morning, 12 hours after pretreatment with lovastatin 40 mg once daily for 3 days. Plasma concentrations of lovastatin increased by approximately 30%.³⁶ The inconsistent results of these 2 studies are most likely due to differences in lovastatin dosage, pretreatment regimens, and grapefruit juice potency.

Administration of a single dose of simvastatin 60 mg after 2 days of pretreatment with 200 mL of doublestrength grapefruit juice administered 3 times daily resulted in a 9- and 7-fold increase in serum concentrations for simvastatin and the metabolite, simvastatin acid.³⁷ The AUC was increased 16- and 7-fold for simvastatin and simvastatin acid, respectively.

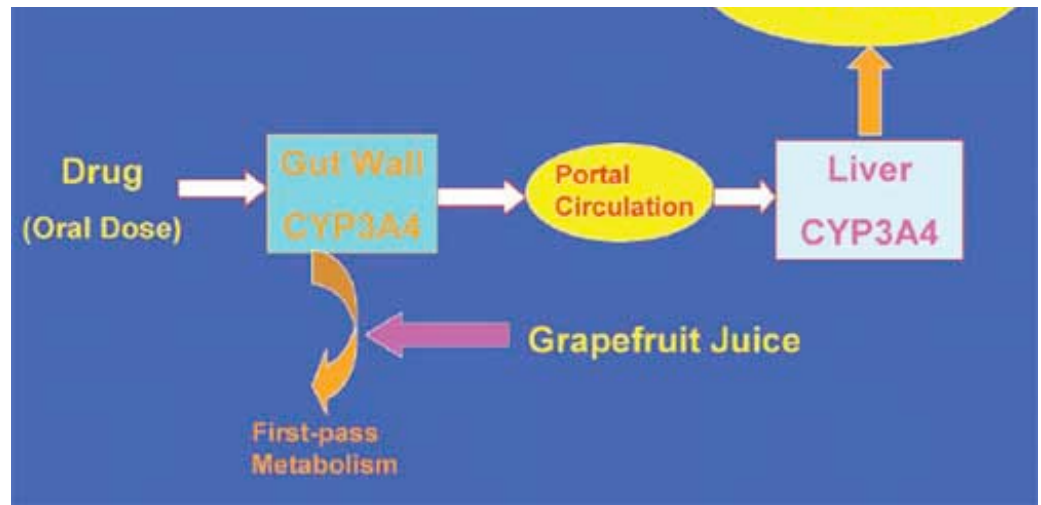
Pretreatment with 200 mL doublestrength grapefruit juice 3 times a day for 2 days resulted a 2.5-fold increase in the AUC of atorvastatin 40 mg.³⁸ In addition, the half-life of atorvastatin was increased from 7.8 hours to 13.3 hours. The AUC of atorvastatin's active metabolites, atorvastatin lactone and 2-hydroxyatorvastatin, are increased approximately 1.3-fold. In a similar study, grapefruit juice had no effect on pravastatin (40 mg) serum concentration or AUC.³⁹

The results of these studies suggest that concomitant administration



Blood
Circulation

of grapefruit juice with atorvastatin, lovastatin, and simvastatin should be avoided. Potentially serious adverse reactions due to elevated levels of statins and metabolites include myalgia and rhabdomyolysis. If this combination cannot be avoided, pharmacists should educate patients on



the symptoms of statin-induced myalgia and rhabdomyolysis (eg, muscle aches, back pain). A safer alternative would be pravastatin. Fluvastatin is not metabolized by CYP3A4 and should not interact, although it has yet to be studied with grapefruit juice.

Grapefruit-Drug Interactions: Reduced Blood Levels

Fexofenadine

Studies also demonstrate that grapefruit juice can reduce blood levels of drugs and possibly reduce efficacy. Fexofenadine is transported into the systemic circulation by OATP. Because grapefruit juice inhibits OATP, blood levels of fexofenadine are reduced.

OTC Medications

Research has yet to uncover clinically significant interactions between grapefruit juice and OTC medications. Caffeine, dextromethorphan, chlorpheniramine, and loratadine, however, may interact to some degree, but because of the wide therapeutic index of these drugs, occasional use of these OTC medications in standard doses with concurrent grapefruit ingestion is not expected to result in significant adverse effects. Caution may be warranted, however, in the elderly and in individuals who may be taking other prescription or nonprescription CYP3A4 inhibitors (eg, cimetidine, clarithromycin, erythromycin, fluvoxamine, itraconazole, ketoconazole, nefazadone, and protease inhibitors such as indinavir, nelfinavir, and ritonavir). Additionally, dietary supplements or botanical products such as St. John's wort may also inhibit CYP3A4 and may result in additive enzyme inhibition with grapefruit.

Public Misinformation

Although the grapefruit-drug interaction was first reported in the scientific literature as

early as the late 1980s, the significance of this interaction was not rapidly recognized by the medical community, and dissemination of accurate information to the public was also inconsistent.⁴⁰ At times, the public received information that was sensationalized and inaccurate. This may have contributed to confusion among patients and pharmacists over the issue of grapefruit-drug interactions. Many patients believed that all drugs interacted with grapefruit juice and stopped drinking grapefruit juice altogether. Other articles incorrectly reported that the interaction could be prevented by separating the drug and the grapefruit juice by 2 hours. A television news story even encouraged patients to drink grapefruit juice to get more out of their medications and save money.⁴¹

Role of the Pharmacist in Communication

The Gallup organization has consistently rated pharmacists at the top or near the top of the most trusted and respected professions. Patients rely on the pharmacist for convenient advice on health issues. A survey of 100 pharmacists nationwide by the Florida Department of Citrus in December 2001 found that nearly 66% of pharmacists had seen an increase in the number of patients seeking information about grapefruit juice-drug interactions, but that only 50% believed they had enough specific information about grapefruit juice interactions.

Pharmacists play an important role in potential grapefruit-drug interaction situations. Patients need accurate, specific information about the grapefruit juice-drug interaction. When educating a patient regarding a potential grapefruit-drug interaction (Table), ask about grapefruit or grapefruit juice consumption. Many fruit juice blends also contain significant amounts of grapefruit juice. Remind patients that most citrus juices such as sweet orange, lemon, citron, and tangerine are considered safe. Sour oranges such as Seville oranges, however, may have an effect similar to grapefruit juice, but these fruits are not used in commercial orange juice production nor are they commonly sold in the United States. Lime juice may also interact. In situations where a patient is taking a medication that interacts with grapefruit juice and does not wish to stop consuming it, the pharmacist might suggest other medication options.

Pharmacists can often predict if a new drug might be a candidate for a significant interaction with grapefruit or its juice by looking at these characteristics:

- Is it metabolized by intestinal CYP3A4?
- Is it given orally?
- Does it have a low bioavailability?
- Does it have a narrow therapeutic index?

The following key messages should be communicated to patients:

- Most medications do not interact with grapefruit juice, but if you consume grapefruit or grapefruit juice let your physician or pharmacist know, especially when beginning a new prescription.
- The effects of OTC products and herbal medications, although believed to be safe based on the current literature, should still be monitored.
- Alternative medications that do not interact with grapefruit may be available if you do not want to stop drinking grapefruit juice or eating grapefruit.

The Future of Grapefruit-Drug Interactions

Many researchers are studying drug interactions with grapefruit to identify the drugs that do and do not interact with grapefruit as well to more clearly elucidate the role of P-gp and OATP in the interaction. In addition, more studies are needed to clarify interactions involving OTC medications and herbal medications.

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