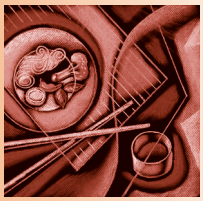

Clinically Significant Grapefruit Juice–Drug Interactions

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Grapefruit juice is typically consumed in the morning at the same time that many patients take their medications. Therefore, there is a concern among healthcare professionals that this may result in clinically significant drug interactions. This article reviews the current understanding of drug–grapefruit juice interactions and those drugs most likely to be affected by the ingestion of grapefruit juice.
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The ability of grapefruit juice to increase drug levels in blood was accidentally discovered during a pharmacokinetic study designed to evaluate an interaction between felodipine (Plendil), a drug prescribed for treatment of hypertension, and ethanol.[1] Double-strength grapefruit juice was used to mask the taste of the ethanol in this randomized, crossover, double-blind study. A nonintoxicating dose of ethanol or placebo was administered to subjects, followed by a 5-mg dose of felodipine. For both study arms, serum felodipine concentrations were noted to be several times greater than that previously reported at that same dose when grapefruit juice was not used. It was then recognized that this finding was possibly due to a pharmacodynamic interaction between grapefruit juice and felodipine.[1] Since this observation, much research has focused on the mechanisms of drug–grapefruit juice interactions and the medications that interact with the juice.

Grapefruit juice is very popular, purchased by 21% of all households in the United States. The United States produces nearly 40% of the world's supply of grapefruit,[2] with Florida being the largest producer, averaging 2 million tons of fruit per year.[3] Grapefruit is endorsed by the American Heart Association as a "heart-healthy food" because it contains compounds that may reduce the formation of artherosclerotic plaques.[4,5] It may also inhibit cancer cell proliferation.[6,7] The compounds in grapefruit juice, however, may also be responsible for clinically significant drug interactions with numerous prescription medications, thus raising potential concern regarding whether it should be consumed at the same time with them. Its effects are most pronounced on cyclosporine, some calcium antagonists, and the hydroxymethylglutaryl–coenzyme A reductase inhibitors. In oral doses of approximately 8 oz, grapefruit juice increases the serum concentrations of these drugs from 1.5- to 15-fold.[5,8] For some drugs such as felodipine and nicardipine, the increased drug concentrations could potentially be associated with an increased frequency of dose-dependent adverse effects,[9,10] although actual reports of toxicity with drug–grapefruit juice interactions have been rare.[11]

The drug–grapefruit juice interaction is caused by inhibition of the intestinal cytochrome P-450 enzyme system, particularly cytochrome P450 3A4 (CYP450 3A4), by 1 or more of the components in grapefruit juice.[8] Many active components in grapefruit juice have been evaluated for potentially causing this interaction, including flavonoids such as naringenin, naringin, quercetin, and kaempferol,[12,13] and nonflavonoids such as 6,7-dihydroxybergamottin, bergaptol, and 6,7-epoxybergamottin.[14,15] Naringin, the glycoside of naringenin, is the most abundant flavonoid in grapefruit juice, constituting up to 10% of its dry weight. Naringin is not found in other citrus or fruit juices and is responsible for the distinctive smell and bitter taste of grapefruit juice. Naringin exerts no effect on the activity of the CYP450 system in vitro, but in vivo, its metabolite, naringenin, is a potent inhibitor of both the CYP 3A and CYP 1A2 isoforms.[16] However, most research suggests the furanocoumarin 6,7-didydroxybergamottin and/or its parent compound bergamottin to be the major CYP 3A4 inhibitors found in grapefruit juice.[17]

Several compounds have been suspected as the culprits in altering metabolism of some drugs.

The concentrations of flavonoids and/or furanocoumarins in grapefruit juice vary considerably depending on the origin, fruit variety, maturity, quality of raw material, manufacturing procedures, and/or storage conditions.[18,19] The amount of active ingredients ingested has an important influence on the mechanism, magnitude, and reproducibility of the grapefruit juice–drug interaction.[20]

Cytochrome P450 Enzyme System

Because grapefruit juice interferes with the cytochrome P450 enzyme system (CYP450) responsible for the metabolism of many drugs, these enzymes and the role they play in drug metabolism will be briefly reviewed.

When some drugs are administered orally, a significant portion of the dose is metabolized to inactive ingredients during "first-pass" metabolism in either the intestinal epithelium or the liver, decreasing the amount of drug reaching the systemic circulation.[21] Therefore, any substance interfering with first-pass metabolism will increase the amount of drug available systemically and possibly cause toxic effects.

Many orally administered drugs are formulated to be lipid soluble and nonpolar in order to enhance their absorption from the gastrointestinal (GI) tract. However, these very properties may hinder a lipophilic drug's elimination from the body; therefore, they may be further metabolized to more polar, water-soluble derivatives, which can be more easily excreted in bile and urine.[21] Drug metabolism is a 2-phase process that typically takes place in the liver, although the GI tract, kidney, and lungs also have significant metabolic activity.[21] In the first phase (phase I), drugs are converted to either active or inactive metabolites mainly through oxidation, reduction, or hydrolysis. Phase I metabolites can then either be excreted directly or undergo additional modification in a second phase II reaction via glucuronidation, sulfation, acetylation, and methylation, which makes them even more hydrophilic and water soluble.[21]

Most important phase I reactions are catalyzed by CYP450 enzymes, a superfamily of iron-containing proteins located on the membrane of the endoplasmic reticulum.[22] These enzymes are found primarily in the liver, but they can also be found in the epithelium of the small intestine and other tissues, where they may also contribute to drug metabolism.[22] The P450 name is based on the fact that the protein has a 450-nm spectral peak via spectrophotometry when carbon monoxide binds to the enzyme in its reduced state.[23] In addition to drugs, these enzymes are responsible for metabolizing endogenous compounds, including fatty acids, prostaglandins, steroids, bile acids, and vitamin D and other compounds, chemicals, and pollutants from the environment.[23]

Nomenclature

Because there are many isoforms or variants of the CYP450 enzymes, a classification system was developed to reduce confusion as to what to call the specific enzymes.[24] The classification of the enzymes is based on how similar amino acid sequences are in particular families and subfamilies, for example, CYP 3A4. The "CYP" designates this as a cytochrome P450 enzyme, and the number that follows signifies the isoform's *family*; isoforms within the same family share more than 40% amino acid identity.[23] The letter following the number identifies the isoform's *subfamily*; isoforms within the same subfamily share more than 55% identity.[23] The final number identifies the *individual enzyme* within the subfamily.[23]

Although 57 cytochrome P450 genes have been identified in humans, only a few play a major role in drug metabolism. These are primarily the CYP 1, CYP 2, and CYP 3 families.[25] The CYP 3A4 enzyme is the most important influence for the metabolism of drugs and is found in abundant quantities in both the liver and the intestinal epithelium.[25] The CYP 3A4 enzyme accounts for approximately 30% of the P450 enzymes in the liver and 70% in epithelial cells of the small intestine.[26] It is estimated that this enzyme is responsible for the metabolism of more than half of the drugs that are metabolized by oxidation.[25] The CYP 2D6 enzyme accounts for approximately 20%, and another 15% to 20% is accounted for by the combination of CYP 2C9 and CYP 2C19.[27] The CYP 2E1, CYP 2A6, and CYP 1A2 enzymes contribute to drug metabolism, but to a lesser extent.[27]

Factors Affecting Enzyme Activity

Many factors, both nongenetic and genetic, affect the CYP450 microsomal enzyme system, influence their activity, and alter drug metabolism. Several drugs interfere with certain CYP450 enzymes by either inhibition (down-regulation of the enzyme) or induction (up-regulation of the enzyme). Drugs that *inhibit* a certain CYP450 microsomal enzyme will reduce the

metabolism of drugs that are substrates for that enzyme, thus prolonging the drugs' presence in the body. Inhibition is generally a result of competition with another drug with the enzyme's binding site.[28] Conversely, drugs that *induce* certain CYP450 enzymes will increase the metabolism of drugs that are substrates for that enzyme and enhance their elimination. Induction occurs when a drug stimulates the production of more enzyme protein, which increases the enzyme's ability to metabolize the drug.[28] Depending on the particular drugs in question and the patient's specific situation, the coadministration of agents metabolized by a specific CYP450 isoenzyme could induce a clinically significant drug interaction.

Genetic factors also may affect a person's capacity to metabolize drugs via CYP450 enzymes. Many of these enzymes are known to be polymorphic, resulting in variations between individuals who are low to high in metabolic capacity. Consequently, for many drugs, individuals are classified into 4 phenotypes: poor metabolizers, intermediate metabolizers, extensive metabolizers, and rapid or ultrarapid metabolizers.[29] These genetic differences may explain why some individuals may be more susceptible to drug interactions than others are.

Mechanisms of Grapefruit Juice–Drug Interactions

Since the discovery that grapefruit juice can alter drug concentrations, a great deal of work has explored the nature and significance of drug–grapefruit juice interactions. The studies do not always agree, causing confusion as to the clinical significance of the problem. In part, the inconsistencies are explained by differences in drug properties, the quantity and specific grapefruit preparation used, and the timing of ingestion of the drug with juice.[30]

Grapefruit juice contains certain compounds (probably flavonoids or furanocoumarins) that inhibit the CYP 3A4 isoforms found in the mucosal lining of the small intestine.[8] Although only those isoforms in the small intestine are usually involved, repeated dosing of 200 to 240 mL (approximately 8 oz) of double-strength grapefruit juice can also inhibit hepatic CYP 3A4 enzymes.[31,32] The other CYP isoforms are not affected to any clinically significant degree; therefore, grapefruit primarily affects only those drugs metabolized by CYP 3A4.[33] Some recent evidence suggests that other CYP450 isoforms such as 2B6 and 3A5 may also be involved,[34] although this finding has not been established clinically. To be affected by grapefruit juice, a drug must also have poor oral bioavailability because there is significant first-pass metabolism due to large quantities of intestinal CYP 3A4.[33] Drugs metabolized by CYP 3A4 that are administered parenterally and thus bypass the GI tract are not affected by drinking grapefruit juice.[20] The magnitude of interaction is highly variable among certain people, which can possibly be explained by differences that exist in enteric CYP 3A4 content.[5] Those individuals with the highest concentrations of intestinal CYP 3A4 are affected the most by grapefruit juice consumption, and this has been shown clinically with felodipine.[35]

Grapefruit juice–related inhibition is a result of an increased degradation of the CYP 3A4 enzyme (mechanism based) and not thought to be caused by a competition with a drug for binding sites.[36] The mechanism-based inhibition occurs after initial competitive binding to the active site on the enzyme. Because the enzyme is degraded, new enzyme synthesis is required for return in metabolic activity, and the recovery half-life after a single glass of juice is approximately 24 hours.[9,37]

Researchers have tried to identify the specific substances in grapefruit juice responsible for the effects on the CYP 3A4 enzyme. Initially, the focus was on naringin, a bioflavonoid that is responsible for the unique smell and bitter taste of grapefruit juice.[38] As noted previously, because naringin is not found in other citrus products, this substance was suspected as the causative agent because more drugs interact with grapefruit juice than with any other citrus product.[38] Naringenin has only mild effects on the CYP 3A4 enzyme in vivo.[18] More recently, research has focused on the 2 furanocoumarins, bergamottin and 67-dihydroxbergamottin, both irreversible inhibitors of the CYP 3A4 and present in grapefruit juice.[39] Seville (sour) oranges contain both compounds and inhibit drugs metabolized by the CYP 3A4 as well.[40] Paine and colleagues[41] recently demonstrated that a furanocoumarin-free grapefruit juice had little effect on the overall bioavailability of felodipine when compared to standard grapefruit juice, suggesting that these substances are primarily responsible for the interaction. There is the possibility that, perhaps, other substances, in conjunction with furanocoumarins, may contribute as well.[39] Additional research is needed to clearly establish the component of grapefruit juice most likely to be the cause of the effects on the CYP 3A4 enzyme.

Another proposed mechanism for grapefruit juice–drug interactions is related to P-glycoprotein (Pgp). This is a protein located in many tissues that serve as barriers, such as the brush border of the small intestine, that acts as an efflux pump to transport various compounds out of cells.[42] Enteric Pgp reduces the bioavailability of substrate drugs by pumping them

from the intestinal cells back into the gut lumen.[38] In addition to inhibiting CYP 3A4, there is some evidence that, perhaps, grapefruit juice also inhibits intestinal Pgp, thus enhancing drug absorption.[43] Because both CYP 3A4 and Pgp share many substrates and inhibitors, it is postulated that inhibition of Pgp by grapefruit juice may augment that of CYP 3A4 inhibition.[44] To explore this possibility in humans, Parker and colleagues[45] conducted a study using digoxin as a probe for Pgp to see if the drug's pharmacokinetics were altered by grapefruit juice. Digoxin was selected because Pgp plays an important role in the absorption, distribution, and excretion of digoxin, and digoxin is not metabolized by CYP 3A4. Because digoxin kinetics were not altered by grapefruit juice, the researchers concluded that inhibition of intestinal Pgp was not a likely mechanism for grapefruit juice interactions. However, digoxin has a relatively high oral bioavailability and may not have been the most appropriate agent to use.[36] Further clinical research is needed to clarify the effect that grapefruit juice has on Pgp.

Grapefruit juice may actually *decrease* the bioavailability of some medications because of its effects on the organic anion transporting polypeptide (OATP). The effects on OATP are opposite that on Pgp in that it is a transporter that facilitates the uptake of certain drugs.[36] Recent evidence suggests that grapefruit juice can inhibit OATP in vitro at a concentration that has insignificant effects on Pgp even at a concentration that is 10-fold higher.[46] This may explain why certain drugs such as fexofenadine (Allegra) and itraconazole (Sporanox) may have a reduced bioavailability when taken with grapefruit juice. The consequence of this interaction may be a suboptimal therapeutic response.

Several, but not all, drugs may be affected.

Although most studies have used fresh grapefruit juice or the reconstituted frozen product, it is proposed that the substances responsible for drug interactions are also present in the pulp, peal, and core of the fruit.[5] A serious case of rhabdomyolitis in a patient taking the cholesterol-lowering medication simvastatin was believed to be precipitated when the patient began eating a whole grapefruit for breakfast.[47] In summary, the effects that grapefruit have on the CYP 3A4 enzyme are variable and depend on whether it is white or pink, where and when it was grown, and whether it is consumed as the whole fruit or as juice.[48]

Clinical Implications of Grapefruit Juice Consumption

Many of the studies concerning grapefruit juice–drug interactions are based on pharmacokinetic data and do not specifically address the clinical significance of the interaction. In addition, the exposure to grapefruit juice in many of these studies was generally limited to approximately 8 oz of grapefruit juice administered 1 to 3 times per day for 2 to 3 days. Caution should be exercised before suggesting that a single serving of juice will have long-term effects on the bioavailability of certain medications and possibly result in adverse reactions.[2] In general, most grapefruit juice–drug interactions are minor and are not clinically significant.[2] However, patients with severe liver impairment, where exposure to the drug would be greater, or with a medical condition that predisposes them to enhanced drug effects may be more susceptible to the interaction.[2,8]

The inhibitory effect of grapefruit juice is partly irreversible. It may last for 24 to 48 hours after a single 8-oz glass.[25] Therefore, taking medications at a different time as drinking the grapefruit juice will not necessarily avoid the interaction.[48] As a rule, drugs that inhibit the CYP 3 will have their effect on the enzyme diminish with recurrent use.[38] However, chronic use of the juice several times a day will produce an additive inhibitory effect and increase the extent of the interaction.[35]

Table 1 lists those medications that are known to interact with grapefruit juice and the potential consequences of the interaction.[5,20,49–68] Note in Table 1 that in some cases, there may be other medications within a particular drug class that can be prescribed as an alternative if there is a strong interaction. For example, even though grapefruit juice interacts with some hydroxymethylglutaryl–coenzyme A reductase inhibitors ("statins"), for others, CYP 3A4 plays only a small role in their metabolism and can be considered as an alternative drug in patients who consume grapefruit juice.

In summary, the clinical significance of drug–grapefruit juice interactions has not been clearly established. This may be due to the fact that many agents affected by grapefruit juice have a wide therapeutic index, with some exceptions such as cyclosporine and carbamazepine.[11] In addition, the nature of the interaction for a specific patient is dependent on the concentration of intestinal CYP 3A4 that patient has.[11] For most medications that

Table 1. Reported Drug–Grapefruit Juice Interactions

Category	Generic (Brand) Name	Nature of Interaction	Comments
Antiarrhythmics	Amiodarone (Cordarone)	Bioavailability increased and decreased in alteration on PR and QTc interval[49]	Prescribing information advises to avoid GFJ[50]
Anticonvulsants	Carbamazepine (Tegretol)	Bioavailability, peak, and trough concentrations increased[51]	Because of narrow therapeutic index, avoid coadministration with GFJ. Observe for dizziness, ataxia, drowsiness, nausea/vomiting, tremor, and agitation.
Antidepressants	Clomipramine (Anafranil)	Increased plasma concentrations[52]	Observe for dry mouth, somnolence, dizziness, and fatigue
Antifungals	Itraconazole (Sporanox)	Absorption decreased[53]	Clinical significance not known. Coadministration with GFJ could decrease efficacy.
Antihistamines	Fexofenadine (Allegra)	Oral absorption decreased[54]	Prescribing information recommends taking with water.[55] Desloratadine (Clarinex) is an alternative.
Antineoplastics	Etoposide (VePesid)	Bioavailability reduced[56]	Possible decrease in effect. Avoid combination until more data are available.
Anxiolytics and sedative hypnotics	Buspirone (Buspar) Diazepam (Valium) Midazolam (Versed) Triazolam (Halcion)	Bioavailability and plasma concentrations increased. Clinically significant interaction with buspirone[57] and diazepam[58] reported	Observe for increased sedation and changes in cognitive function. Other benzodiazepine sedative hypnotics such as alprazolam (Xanax) and lorazepam (Ativan) are well absorbed and not likely to interact with GFJ.[5]
Calcium channel blockers	Felodipine (Plendil) Nicardipine (Cardene) Nifedipine (Procardia) Nimodipine (Nimotop) Nisoldipine (Sular)	Bioavailability and peak serum concentrations increased.[1,59–64] Pharmacodynamic changes (heart rate, blood pressure) reported after GFJ was administered with felodipine[9]	Observe for flushing, headache, tachycardia, and hypotension. Amlodipine(Norvasc), diltiazem (Cardizem), and verapamil (Calan) may be considered alternatives from this drug class because they have a small or negligible interaction.[2]
Erectile dysfunction	Sildenafil (Viagra)	Bioavailability increased[65]	No adverse effects noted, but blood pressure and heart rate could increase. GFJ interaction could theoretically be seen with tadalafil (Cialis) and vardenafil (Levitra).[20]
HMG-CoA reductase inhibitors (''Statins'')	Atorvastatin (Lipitor) Lovastatin (Mevacor) Simvastatin (Zocor)	Bioavailability increased. Minimal effect on pharmacodynamics[20]	Observe for headache, gastrointestinal complaints, hepatic inflammation, and muscle pain. Fluvastatin (Lescol), pravastatin (Pravacol), and rosuvastatin (Crestor) are not affected.[20]
Immunosuppressants	Cyclosporine (Sandimmune, Neoral)	Increase in bioavailability and serum concentrations[66]	Coadministration with GFJ has been proposed to reduce cost of cyclosporine therapy. However, interaction is unpredictable, and administration with GFJ not advised.[5]

(continues)

Table 1. (continued)

Category	Generic (Brand) Name	Nature of Interaction	Comments
Opioid analgesics	Methadone (Methadose)	Increases peak levels and overall bioavailability[67]	Clinical significance not established. Observe for respiratory depression, decreased cognitive function, and increased sedation.
Protease inhibitors	Saquinavir (Invirase)	Oral bioavailability increased. Interaction considered weak[68]	Observe for increased headache, fatigue, insomnia, and anxiety.

Abbreviations: GFJ, grapefruit juice; HMG-CoA, hydroxymethylglutaryl–coenzyme A.

are metabolized by the CYP 3A4 enzyme, limiting grapefruit juice consumption to 8 oz per day would most likely not present any clinical consequences.[48]

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