OATP Fruit Juice Drug Interactions

Background
Grapefruit juice has been shown to increase plasma levels of several medications through CYP3A4 inhibition. These interactions have been reviewed in the medical literature and even covered by the lay media. Now allergy medication advertisements in the U.S. are highlighting an interaction between Allegra (fexofenadine) and other fruit juices. This interaction, which leads to decreased levels of fexofenadine, is caused by fruit juice inhibition of an organic anion transporting peptide (OATP) in the gut. This article reviews OATP and other drug transporters, with an emphasis on drug interactions caused by OATP inhibition by fruit juices.

Drug Transporters
There are two main families of drug transporters. One is comprised of P-glycoprotein (multidrug resistance protein 1 [MDR1]) and its relatives, multidrug resistance-associated protein, breast cancer resistance protein, and bile salt export pump. P-glycoprotein is found in cancer cells where it causes resistance to chemotherapy. It is also found in the gut, liver, kidney, and blood-brain barrier. P-glycoprotein transports drugs from enterocytes into the intestinal lumen, and from hepatocytes into the bile for elimination. P-glycoprotein can be thought of as a defense against potential poisons.

In opposition to P-glycoprotein, which is an efflux pump, are organic anion transporting polypeptides (OATPs), which are uptake transporters. OATPs transport drugs into cells, enhancing drug absorption. Like p-glycoprotein, they are located in the gut, liver, kidney, and blood-brain barrier. Several OATPs have been identified, such as OATP1A2 and OAT2B1.

Patients can have varying OATP activity due to genetic variation. For example, reduced responsiveness to montelukast (Singular) is associated with a variant of the gene coding for OAT2B1. Such genetic variation can influence susceptibility to drug interactions. For example, OATP inhibition may not be significant in patients with impaired baseline OATP function.

Drug Interactions
Examples of drugs transported by p-glycoprotein (i.e., p-glycoprotein substrates) include cyclosporine, digoxin, fexofenadine, paclitaxel, saquinavir, and vinblastine. Examples of p-glycoprotein inhibitors include itraconazole, lopinavir, ritonavir, verapamil, and grapefruit juice. These inhibitors have the potential to increase levels of p-glycoprotein substrates. P-glycoprotein inducers include carbamazepine, rifampin, and St. John’s wort. These inducers have the potential to decrease levels of p-glycoprotein substrates.

P-glycoprotein, CYP3A4, and OATP substrates, inhibitors, and inducers overlap somewhat. P-glycoprotein and CYP3A4 are both found in the gut and liver and are thought to work together to prevent drug absorption. But OATP has the opposite function. However, commonalities in substrates, inhibitors, and inducers pose challenges in studying drug interaction mechanisms and predicting the net effect of drug interactions. For example, grapefruit juice is an inhibitor of CYP3A4 as well as OATP2B1. If drug is a substrate of both CYP3A4 and OATP2B1 (e.g., montelukast), grapefruit juice could decrease its absorption by inhibiting OATP and block its metabolism by inhibiting CYP3A4. There may therefore be little net effect on drug plasma level. Because fexofenadine is a substrate of OATP1A2, but not p-glycoprotein or CYP3A4, it has been used to study drug interactions mediated by OATP1A2.

Because OATP1A2 aids drug absorption, inhibiting OATP1A2 potentially decreases serum levels of the drugs it transports (e.g., acebutolol, atenolol, ciprofloxacin, fexofenadine,.
levofloxacin, levothyroxine). Several fruit juices contain constituents that inhibit OATP. These include grapefruit juice, orange juice, and apple juice. The effect of fruit juices on OATP seems to last no longer than four hours.\textsuperscript{1,5} This is different from the inhibition by grapefruit juice of intestinal CYP3A4, which can last several days.\textsuperscript{3} The magnitude of the effects of grapefruit, orange, and apple juice on OATP appear to be similar and can be significant with a 200 mL (6.8 ounces) serving.\textsuperscript{1,5}

OATP2B1 substrates include glyburide and aliskiren (e.g., Tekturna\textsuperscript{[U.S.]}, Rasilez\textsuperscript{[Canada]}). But clinically, glyburide does not seem to be affected by grapefruit juice. This suggests that although glyburide is an OAT2B1 substrate, it is not significantly dependent upon OAT2B1 for absorption. Perhaps it is lipophilic enough to be absorbed passively.\textsuperscript{1} However, absorption of aliskiren (Tekturna) a hydrophilic drug, is decreased to a clinically significant extent by both orange and apple juice.\textsuperscript{5} Although the OATP pathway is involved in the absorption of some statins, no clinically significant OATP-mediated interactions between statins and grapefruit or other fruit juice have been identified.\textsuperscript{2,9}

\textbf{Conclusion}

The following table provides a summary of OATP substrates whose absorption has been shown to be decreased by at least 200 to 600 mL of either grapefruit, orange, or apple juice:\textsuperscript{1-3,5,6}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Decrease in Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>acebutolol</td>
<td>7%</td>
</tr>
<tr>
<td>atenolol*</td>
<td>40%</td>
</tr>
<tr>
<td>aliskiren*</td>
<td>about 60%</td>
</tr>
<tr>
<td>ciprofloxacin*</td>
<td>about 20%</td>
</tr>
<tr>
<td>fexofenadine*</td>
<td>about 40%</td>
</tr>
<tr>
<td>levofloxacin*</td>
<td>7%</td>
</tr>
<tr>
<td>levothyroxine</td>
<td>11%</td>
</tr>
<tr>
<td>montelukast**</td>
<td>0 to 22%</td>
</tr>
</tbody>
</table>

*Atenolol, ciprofloxacin, and levofloxacin not studied with grapefruit juice.

**Montelukast was studied with grapefruit juice and no effect was observed.\textsuperscript{5}

A decrease in absorption of 10\% or less is unlikely to be significant in most patients.\textsuperscript{2,7} For those drugs that may be significantly affected, instruct patients to avoid apple, grapefruit, or orange juice within four hours of these medications, or consider an alternative medication that does not interact with fruit juice.\textsuperscript{3} It should be noted that the U.S. Allegra product labeling recommends taking fexofenadine with water.\textsuperscript{8} Also, there is currently no evidence that eating these fruits causes clinically significant OATP-mediated drug interactions.

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\textbf{Project Leader in preparation of this PL Detail-Document: Melanie Cupp, Pharm.D., BCPS}

\textbf{References}


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## Potential Drug Interactions with Grapefruit

(First modified May 2011)  
—Only drugs specifically studied with grapefruit are included.  Other CYP3A4 or organic anion transporting peptide (OATP) substrates might also interact—

### Note:  “AUC” refers to area under the plasma concentration vs time curve and is an indicator of bioavailability

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Findings</th>
<th>Implications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol (Sectral)</td>
<td>Can decrease AUC by 7% by inhibiting organic anion transporting polypeptide (OATP).83</td>
<td>Not likely significant. If concerned, separate by four hours.83</td>
</tr>
<tr>
<td>Aliskiren ([Tekturna [U.S.], Rasilez [Canada])</td>
<td>Can decrease AUC by 60% by inhibiting organic anion transporting polypeptide (OATP).19</td>
<td>May reduce antihypertensive efficacy.19 Separate by four hours.83</td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>No effect.49</td>
<td>None.</td>
</tr>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>Increases AUC by 50% and peak by 84%.46</td>
<td>Prescribing information advises to avoid grapefruit.46,78</td>
</tr>
<tr>
<td>Amprenavir (Agenerase)</td>
<td>Slightly reduces peak and slightly delays time to peak.51</td>
<td>Probably not clinically significant.60</td>
</tr>
<tr>
<td>Benzodiazepines, oral:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam ([Valium])</td>
<td>Increases AUC and plasma concentrations by inhibiting the intestinal metabolism by CYP3A4. No interaction seen with IV midazolam.1-3 Alprazolam does not appear to interact.55</td>
<td>Watch for possible increased sedation. U.S. prescribing information for midazolam syrup advises avoiding grapefruit.67 Some references advise avoiding grapefruit with those benzodiazepines listed.59</td>
</tr>
<tr>
<td>Midazolam ([Versed])</td>
<td></td>
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<tr>
<td>Quazepam ([Doral])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam ([Halcion])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide (Entocort EC)</td>
<td>Increases oral absorption.47</td>
<td>Watch for hypercorticism. Prescribing information advises avoiding grapefruit.47,78</td>
</tr>
<tr>
<td>Buspirone (BuSpar)</td>
<td>Increases absorption and plasma concentrations.4</td>
<td>Despite significant pharmacokinetic effects, the action of the drug does not appear to be affected significantly. Prescribing information advises against drinking large amounts of grapefruit juice.69,78</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Decreases caffeine clearance.1</td>
<td>Watch for possible increase in side effects, such as nervousness or insomnia.</td>
</tr>
<tr>
<td>Calcium Channel Blockers:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine ([Norvasc])</td>
<td>Increases AUC and serum concentrations, most likely the result of grapefruit inhibiting the intestinal metabolism by CYP3A4.1,5-13 No data for isradipine (DynaCirc). (Some references dispute the clinical relevance of the interactions with amlodipine, diltiazem, and verapamil.9,10 However, there is considerable interindividual variability in the effect of grapefruit on drug metabolism.)</td>
<td>Look for signs of toxicity, such as flushing, headache, tachycardia, and hypotension. U.S. prescribing information advises avoiding grapefruit in patients on nisoldipine, nifedipine capsules, and Adalat CC.72-74,81 No studies with Procardia XL. Per Canadian monograph, avoid grapefruit with felodipine, nifedipine, nimodipine, and verapamil.82</td>
</tr>
<tr>
<td>Diltiazem ([Cardizem])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felodipine ([Plendil])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine ([Cardene])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine ([Procardia, Adalat])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nisoldipine ([Sular])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil ([Calan, Verelan, etc])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug(s)</td>
<td>Findings</td>
<td>Implications*</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Carbamazepine (<em>Tegretol</em>)</td>
<td>Increases AUC, peak, and trough plasma concentrations.6</td>
<td>Look for signs of toxicity, such as dizziness, ataxia, drowsiness, nausea, vomiting, tremor, and agitation.</td>
</tr>
<tr>
<td>Carvedilol (<em>Coreg</em>)</td>
<td>Increases bioavailability of a single dose by 16%.14</td>
<td>The clinical significance of this interaction is not known.</td>
</tr>
<tr>
<td>Cilostazol (<em>Pletal</em>)</td>
<td>Increases peak.62</td>
<td>Clinical significance unknown.</td>
</tr>
<tr>
<td>Cisapride (<em>Propulsid</em>)</td>
<td>Increases AUC.46,57</td>
<td>Contraindicated with grapefruit per U.S. prescribing information.70</td>
</tr>
<tr>
<td>Clarithromycin (<em>Biaxin</em>)</td>
<td>Slightly delays absorption.59</td>
<td>Not likely significant.</td>
</tr>
<tr>
<td>Clomipramine (<em>Anafranil</em>)</td>
<td>Increases plasma concentrations.15</td>
<td>Watch for possible increase in side effects, such as dry mouth, somnolence, dizziness, fatigue.</td>
</tr>
<tr>
<td>Clozapine (<em>Clozaril</em>)</td>
<td>No effect.49</td>
<td>None.</td>
</tr>
<tr>
<td>Cyclosporine (<em>Neoral, Sandimmune</em>)</td>
<td>Increases AUC and serum concentrations.16</td>
<td>Look for signs of toxicity, such as nephrotoxicity, hepatotoxicity, and increased immunosuppression. Prescribing information advises avoiding grapefruit.58,78</td>
</tr>
<tr>
<td>Desloratadine (<em>Clarinex</em>)</td>
<td>No effect.49</td>
<td>None.</td>
</tr>
<tr>
<td>Dextromethorphan (e.g., <em>Robitussin DM</em>)</td>
<td>AUC increased.54</td>
<td>Watch for drowsiness.</td>
</tr>
<tr>
<td>Digoxin (<em>Lanoxin</em>)</td>
<td>Slight increase in AUC.48</td>
<td>Unlikely significant with occasional consumption of a glass of juice.48</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Increases AUC and peak.51</td>
<td>Theoretical concern for QT prolongation and torsades de pointes.</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Increases absorption and plasma concentrations of 17-beta-estradiol and ethinyl estradiol17,18</td>
<td>Effects are unknown at this time.</td>
</tr>
<tr>
<td>Etoposide (e.g., <em>Vepesid</em>)</td>
<td>Impairs absorption.83 Mechanism unknown.83</td>
<td>Given that this is a chemotherapeutic agent, decreased AUC is concerning.83 Avoid combination.</td>
</tr>
<tr>
<td>Fexofenadine (<em>Allegra</em>)</td>
<td>Can decrease AUC by about 40% by inhibiting organic anion transporting polypeptide (OATP).83,89</td>
<td>The clinical significance of this interaction is unknown. U.S. labeling recommends taking fexofenadine with water.75 Separate by four hours to be safe.83 Consider desloratadine (<em>Clarinex</em>) as alternative.</td>
</tr>
<tr>
<td>Fluvoxamine (<em>Luvox</em>)</td>
<td>Peak and AUC increased.92</td>
<td>Watch for nausea.</td>
</tr>
</tbody>
</table>
### Drug(s)

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Findings</th>
<th>Implications*</th>
</tr>
</thead>
</table>
| **HMG-CoA Reductase Inhibitors:**  
  Atorvastatin (**Lipitor**)  
  Lovastatin (**Mevacor**)  
  Simvastatin (**Zocor**) | Increases absorption and plasma concentrations by inhibiting gut CYP3A4 metabolism.  
  Look for increased toxicity, such as headache, GI complaints, and muscle pain.  
  Lovastatin (**Mevacor**) and simvastatin (**Zocor**) prescribing information say up to a quart/liter of juice daily is o.k.  
  But other experts suggest avoiding grapefruit with atorvastatin (**Lipitor**), simvastatin, and lovastatin.  
  Consider pravastatin (**Pravachol**) (not affected), rosuvastatin (**Crestor**), or fluvastatin (**Lescol**) as alternatives (not metabolized by CYP3A4). |               |
| **Haloperidol (**Haldol**)** | No significant effect.                                                   | None.         |
| **Indinavir (**Crixivan**)** | Slightly delays absorption.                                              | Unknown significance. |
| **Itraconazole (**Sporanox**)** | May decrease AUC.                                                       | The clinical significance of this interaction is unknown. |
| **Levothyroxine** | Can decrease AUC by 11% by inhibiting the organic anion transporting polypeptide (OATP). | Separate by four hours. |
| **Losartan (**Cozaar**)** | Might reduce the AUC of the major active metabolite.                    | Might reduce the effectiveness of losartan, but further studies are needed to determine significance. Candesartan (**Atacand**), eprosartan (**Teveten**), telmisartan (**Micardis**), and valsartan (**Diovan**) effects could theoretically be increased. Watch for hypotension, dizziness, tachycardia, syncope, and hyperkalemia. |
| **Methadone (**Dolophine**)** | Increases peak and AUC.                                                 | Clinically significant effect unlikely, but cannot be ruled out; best to avoid combination. |
| **Methylprednisolone, oral** | Increases plasma concentration and half-life of oral methylprednisolone. | Consumption of large amounts of grapefruit might increase the risk of adverse effects. |
| **Montelukast (**Singulair**)** | No effect.                                                              | None.         |
| **Nilotinib (**Tasigna**)** | Increases peak by 60% and AUC by 29%.                                   | Prescribing information advises to avoid grapefruit. |
| **Omeprazole (**Prilosec**)** | No significant effect.                                                 | None.         |
| **Phenytoin (**Dilantin**)** | No effect.                                                              | None.         |
| **Progesterone (e.g., **Prometrium**)** | Increases AUC.                                                         | Unknown.      |
| **Quinidine** | Decreases drug clearance, prolongs the half-life, and delays absorption. | The clinical significance of this interaction is unknown. |
| **Quinine** | No effect.                                                              | None.         |
| **Saquinavir (**Fortovase**, **Invirase**)** | Increases absorption and plasma concentrations. | Watch for possible increase in side effects, such as fatigue, headache, insomnia, anxiety. |
| **Scopolamine (**Scopace**)** | Increases absorption and plasma concentrations. | Unknown.      |
| **Sertraline (**Zoloft**)** | Increases serum concentrations.                                         | The clinical significance of this interaction is unknown. |
Drug(s) | Findings | Implications*
---|---|---
Sildenafil (e.g., *Viagra*) | Increases AUC.\(^{48}\) | Adverse events not seen in study, but decreased blood pressure and increased heart rate could occur in some patients. Interaction could theoretically occur with tadalafil (*Cialis*) and vardenafil (*Levitra*).\(^{48}\) (Avoid grapefruit per Canadian *Levitra* prescribing info).\(^{78}\)
Tacrolimus (*Prograf*) | Increases trough.\(^{54}\) | Look for signs of toxicity, such as hypertension, tremor, headache, insomnia. Prescribing information advises to avoid grapefruit.\(^{64,78}\) Interaction theoretically possible with sirolimus (*Rapamune*); avoid grapefruit per prescribing information.\(^{78,80}\)
Telithromycin (*Ketek*) | No effect.\(^{71}\) | None.
Theophylline (e.g., *Theo-Dur*) | Decreases AUC and peak, and delays time to peak.\(^{49,61}\) | Monitor levels or avoid.\(^{61}\)
Warfarin (*Coumadin*) | No effect up to three glasses (24 oz) daily. Case report of increased INR associated with 50 oz daily.\(^{63}\) | Limit grapefruit juice intake to three glasses daily.

* Many of these interactions have been documented by observing serum concentration changes without alteration of the responses to the drugs. Because of this and the variability in these interactions, clinicians should consider the above listing as potential interactions and monitor patients accordingly. To avoid any potential interaction, have patients avoid eating grapefruit or drinking grapefruit juice while on these medications.

**Background**

Grapefruit juice has been shown to affect the metabolism of several drugs.\(^{29,30}\) Included in the list of potential target drugs are diazepam, cisapride, cyclosporine, felodipine and other dihydropyridine calcium channel blockers, midazolam, nisoldipine, triazolam, saquinavir, lovastatin, and atorvastatin. The mechanism of the drug-drug interaction appears to primarily result from inhibition of CYP3A4 in the intestinal wall and is most important for drugs with high first pass metabolism.\(^{29}\) Large amounts may also inhibit CYP450 in the liver.\(^{48}\) Other mechanisms that might also be involved include inhibition of intestinal P-glycoprotein and organic anion transporting peptide (OATP).

P-glycoprotein is a drug transporter that is present at high levels in the intestinal mucosa.\(^{38}\) It inhibits the absorption and increases the excretion of drugs. Researchers are now suggesting that grapefruit juice might be an inhibitor of P-glycoprotein, mainly in the gut.\(^{39,40,49}\) There is some evidence that grapefruit might also inhibit the transporter OATP at the intestinal level.\(^{41}\) This transporter, unlike P-glycoprotein, transports substances into cells. More research is needed to determine the significance of the OATP interaction.

Several constituents of grapefruit juice have been implicated including the flavonoids naringin and naringenin, along with the furanocoumarins, bergapten and 6,7-dihydroxybergamottin.\(^{29,31,42,43}\) Unfortunately, the content of these varies between different grapefruit juices and varieties of fruit, making it impossible to determine if one is safer than another.\(^{32,43}\)

**How Long Does the Inhibition Last?**

Takanaga et al (2000) performed a study to clarify how long grapefruit juice inhibits intestinal CYP3A4.\(^{33}\) They used oral nisoldipine because it fits the characteristics of a drug that would be susceptible to this interaction. The study group included eight healthy subjects. None were taking any drugs that would affect CYP3A4, and two were smokers. Each subject underwent six trials, each separated by at least one week. The trials are described below:

1. Control: 10 mg nisoldipine with water
2. G0: 5 mg nisoldipine with 200 mL grapefruit juice
3. G14: 5 mg nisoldipine 14 hours after 7 days of TID grapefruit juice
4. G38: 5 mg nisoldipine 38 hours after 7 days of TID grapefruit juice
5. G72: 5 mg nisoldipine 72 hours after 7 days of TID grapefruit juice
6. G96: 5 mg nisoldipine 96 hours after 7 days of TID grapefruit juice

During the seven-day grapefruit juice administration, it was ingested at 9 a.m., 1 p.m., and 7 p.m. For G14-G96 the drug was ingested at the indicated number of hours after the last ingestion of grapefruit juice. Pharmacokinetics variables were determined after serum sampling for nisoldipine to determine Cmax, tmax, t1/2, and AUC. The pharmacodynamic impact was evaluated by monitoring heart rate and blood pressure for the maximal effect (Emax) and area under the effect (AUE) curve. Adverse effects were monitored by asking the subjects for spontaneous reports and open questioning.

Systolic and diastolic blood pressures were significantly decreased for eight hours after the dose in the G0 condition. The effects varied in the other study conditions. The systolic blood pressure was still significantly decreased in the G38 condition, and the diastolic AUE was still significantly decreased in the G72 condition. Adverse events were spontaneously reported in each treatment. Headaches were reported by three subjects in G0, two in G14, and one in G38.

The pharmacokinetics of nisoldipine were significantly altered by grapefruit juice. The plasma concentration was significantly elevated in the G0 to G72 groups. Cmax was significantly elevated in G0 and G14. In contrast, neither tmax nor t1/2 were significantly altered by grapefruit juice. The authors of this study concluded that it would be necessary to withhold grapefruit juice for at least three days before administration of this drug in order to avoid a drug interaction.

**Commentary**

The maximal impact of the first dose in this study agrees with a recent study looking at felodipine. Near maximum inhibition of gut CYP3A4 occurs with just 200 mL (less than a typical serving), and even lesser amounts can interact.

This study gives a clearer picture of the duration of the impact of grapefruit juice on CYP3A4 activity. The pharmacokinetic parameters appear to be affected for at least three days following ingestion, and could perhaps be longer in some patients.

In the Takanaga et al study, the pharmacodynamic impact did last up to 72 hours, but effects declined after ingestion as time went on and were much greater in the situation where the drug was taken with the grapefruit juice. Another study in healthy volunteers found that after a single 300 mL serving, half the gut enzymes had recovered after 23 hours. This might be enough recovery to prevent a clinically significant interaction in some patients. But for others, it may take longer for normal metabolism to return. The only way to avoid this interaction is to advise patients to not ingest grapefruit juice.

Grapefruit juice does not normally inhibit the pharmacokinetics of medications administered intravenously. At usual doses it only affects enzymes in the gut wall. However, high consumption could inhibit liver CYP3A4 and prolong drug half-life.

In addition to grapefruit juice, many researchers are warning that the fruit itself could also cause problems. Several studies now indicate that the fruit should also be avoided in patients taking interacting drugs. Health Canada is now advising consumers NOT to drink grapefruit juice or eat grapefruit in any form if they are taking medications that might interact, until they have talked to their doctor or pharmacist about the potential for side effects.

While sweet oranges and their juice do not appear to cause the same reaction, sour orange juice, such as that from Seville oranges, may have an effect similar to grapefruit juice. However, Seville orange juice is unpalatable, so Seville oranges are more often consumed as marmalade. Preliminary research suggests lime juice might also have this effect. Tangelos are a hybrid of grapefruit and may also interfere with drugs. Most other citrus fruits, such as lemons, citrons, naturally sweet oranges, and tangerines are considered safe. There’s no proof citrus or grapefruit-flavored sodas interact.

Most adverse events resulting from grapefruit interactions have been minor. However, attempts to classify interactions as “mild,” “moderate,” or “severe” may be misleading. This is because the

*More...*
clinical significance of grapefruit juice interactions is likely to vary from patient-to-patient. Factors that may affect response include the patient’s intestinal CYP3A4 content, age, and medical conditions. For this reason, empiric dosage adjustment in an effort to avoid the interaction may not be effective. Instead, advise patients taking potentially interacting drugs to avoid grapefruit [Evidence level C; expert opinion]. If a patient insists on grapefruit, consider an alternative drug known not to interact.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Project Leaders in preparation of this Detail-Document: Melanie Cupp, Pharm.D., BCPS (January 2007 update), William A. Kehoe, Pharm.D., MA, FCCP, BCPS (original author)

Levels of Evidence
In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
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| A     | High-quality randomized controlled trial (RCT)  
High-quality meta-analysis (quantitative systematic review) |
| B     | Nonrandomized clinical trial  
Nonquantitative systematic review  
Lower quality RCT  
Clinical cohort study  
Case-control study  
Historical control  
Epidemiologic study |
| C     | Consensus  
Expert opinion |
| D     | Anecdotal evidence  
In vitro or animal study |


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