

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Patients should discontinue grapefruit consumption for 72 hours before use of a drug that may interact with it.	C	5, 6	The potential for a grapefruit-drug interaction persists for up to 72 hours according to one study. ⁵
Potential grapefruit-drug interactions cannot be avoided by separating times of medication administration and grapefruit consumption.	C	5, 6	Studies have shown that consuming 8 oz of grapefruit juice may decrease the concentration of intestinal cytochrome P450 3A4 by 47 percent for 24 to 72 hours.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 542 or <http://www.aafp.org/afpsort.xml>.

CYP 3A4 is affected, the interaction will only occur with oral formulations. Studies of the intravenous form of drugs that are substrates of hepatic CYP 3A4 and have the potential to interact with grapefruit failed to demonstrate any effect on plasma concentration.⁴

Medications metabolized by intestinal CYP 3A4 that have a low oral bioavailability or a narrow therapeutic index are more likely to have clinically significant interactions with grapefruit products.⁹ Because medications metabolized extensively by intestinal CYP 3A4 generally have low oral bioavailability, and because grapefruit inhibits this metabolic pathway, higher plasma concentrations of these medications will result. Furthermore, if the medication has a narrow therapeutic index, small increases in plasma concentration may cause drastic increases in therapeutic or adverse effects.⁹

MANAGEMENT

When considering how to manage grapefruit-drug interactions, a physician should first decide if the interaction is clinically relevant. A number of medications (e.g., angiotensin receptor blockers, buspirone [BuSpar], estrogens, fexofenadine [Allegra], itraconazole [Sporanox], sildenafil [Viagra], triazolam [Halcion], warfarin [Coumadin]) reportedly or theoretically interact with grapefruit. However, many of these interactions have not been proven clinically significant, or inconsistent data

exist.¹⁰⁻¹⁸ *Table 1*^{9,19-30} describes medication classes that have had documented, clinically significant interactions with grapefruit products, and possible alternative therapies for these drugs.

The importance of clearly understanding possible interactions between drugs and grapefruit products is becoming more evident. The manufacturers of cyclosporine (Sandimmune, Neoral) and simvastatin (Zocor) have gone so far as to place warnings on their drugs' package inserts.^{25,31,32}

Members of various family medicine departments develop articles for "Clinical Pharmacology." This is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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Patients should avoid grapefruit products for 72 hours before taking a drug with which they may interact.

TABLE 1
Grapefruit-Drug Interactions and Alternative Therapies

Drug class	Drugs potentially affected by grapefruit	Effects of interaction	Alternative treatments
Antiarrhythmics	Amiodarone (Cordarone), disopyramide (Norpace), quinidine	Increased plasma concentrations of amiodarone may cause thyroid or pulmonary toxicity, liver injury, QTc prolongation, proarrhythmic disorders, and bradycardia. ¹⁹ Increased plasma concentration of quinidine and disopyramide may be cardiotoxic causing torsades de pointes. ^{9,20}	Digoxin (Lanoxin), diltiazem (Cardizem), verapamil (Calan) Beta blockers
Calcium channel blockers	Felodipine (Plendil), nifedipine (Procardia), nimodipine (Nimotop), nisoldipine (Sular)	Increased plasma concentration may lead to flushing, peripheral edema, headaches, tachycardia, symptomatic hypotension, and myocardial infarction in rare cases. ⁹	Amlodipine (Norvasc), diltiazem (Cardizem), verapamil (Calan)
Statins	Atorvastatin (Lipitor), lovastatin (Mevacor), simvastatin (Zocor)	Increased plasma concentration may cause headaches, gastrointestinal complaints, hepatic inflammation, and myopathies (e.g., rhabdomyolysis). ²¹⁻²⁴	Fluvastatin (Lescol), pravastatin (Pravachol), rosuvastatin (Crestor) Fibric acids, nicotinic acid, or bile acid sequestrants
Immunosuppressants	Cyclosporine (Sandimmune, Neoral), tacrolimus (Prograf)	Increased drug exposure without effects on peak concentration may cause increased adverse events or toxicity evidenced by renal toxicity, hepatic toxicity, and increased immunosuppression. ²⁵⁻²⁹	No alternatives available
Protease inhibitors	Saquinavir (Fortovase)	Increased plasma concentrations may cause increased side effects such as headache, fatigue, insomnia, and anxiety. ³⁰	Amprenavir (Agenerase), atazanavir (Reyataz), fosamprenavir (Lexiva), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir)

Information from references 9 and 19 through 30.

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