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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.[1] 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.[1]

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.[1]

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.[1] Like p-glycoprotein, they are located in the gut, liver, kidney, and blood-brain barrier.[2] Several OATPs have been identified, such as OATP1A2 and OAT2B1.[1]

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.[3]

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.[1]

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.[3] Because fexofenadine is a substrate of OATP1A2, but not p-glycoprotein or CYP3A4, it has been used to study drug interactions mediated by OATP1A2.[1]

Because OATP1A2 aids drug absorption, inhibiting OATP1A2 potentially decreases serum levels of the drugs it transports (e.g., acebutolol, atenolol, ciprofloxacin, fexofenadine,

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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.[1,5] This is different from the inhibition by grapefruit juice of intestinal CYP3A4, which can last several days.[4] 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.[1,5]

OATP2B1 substrates include glyburide and aliskiren (e.g., *Tekturna* [U.S.], *Rasilez* [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.[1] However, absorption of aliskiren (*Tekturna*) a hydrophilic drug, is decreased to a clinically significant extent by both orange and apple juice.[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.[2,9]

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:[1-3,5,6]

Drug	Decrease in Absorption
acebutolol	7%
atenolol*	40%
aliskiren	about 60%
ciprofloxacin*	about 20%
fexofenadine	about 40%
levofloxacin*	7%
levothyroxine	11%
montelukast**	0 to 22%

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

**Montelukast was studied with grapefruit juice and no effect was observed.[3]

A decrease in absorption of 10% or less is unlikely to be significant in most patients.[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.[3] It should be noted that the U.S. *Allegra* product labeling recommends taking fexofenadine with water.[8] Also, there is currently no evidence that eating these fruits causes clinically significant OATP-mediated drug interactions.

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References

1. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *Br J Clin Pharmacol* 2010;70:645-55.
2. Greenblatt DJ. Analysis of drug interactions involving fruit beverages and organic anion-transporting polypeptides. *J Clin Pharmacol* 2009;49:1403-7.
3. Mougey EB, Lang JE, Wen X, Lima JJ. Effect of citrus juice and SLCO2B1 genotype on pharmacokinetics of montelukast. *J Clin Pharmacol* 2011;51:751-60.
4. *PL Detail-Document*, Potential Drug Interactions With Grapefruit. *Pharmacist's Letter/Prescriber's Letter.* February 2007.
5. Tapaninen T, Neuvonen PJ, Niemi M. Orange and apple juice greatly reduce the plasma concentrations of the OATP2B1 substrate aliskiren. *Br J Clin Pharmacol* 2011;71:718-26.
6. Dresser GK, Bailey DG, Leake BF, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. *Clin Pharmacol Ther* 2002;71:11-20.
7. FDA. Therapeutic equivalence of generic drugs-response to National Association of Boards of Pharmacy. April 16, 1998. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073224.htm. (Accessed May 5, 2011).
8. *Allegra* product labeling. http://allegra.com/allegra_family.aspx. (Accessed May 12, 2011).
9. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* 2009;158:693-705.

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Potential Drug Interactions with Grapefruit

(Last 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

Drug(s)	Findings	Implications*
Acebutolol (*Sectral*)	Can decrease AUC by 7% by inhibiting organic anion transporting polypeptide (OATP).[83]	Not likely significant. If concerned, separate by four hours.[83]
Aliskiren (*Tekturna* [U.S.], *Rasilez* [Canada])	Can decrease AUC by 60% by inhibiting organic anion transporting polypeptide (OATP).[19]	May reduce antihypertensive efficacy.[19] Separate by four hours.[83]
Amitriptyline (*Elavil*)	No effect.[49]	None.
Amiodarone (*Cordarone*)	Increases AUC by 50% and peak by 84%.[46]	Prescribing information advises to avoid grapefruit.[46,78]
Amprenavir (*Agenerase*)	Slightly reduces peak and slightly delays time to peak.[61]	Probably not clinically significant.[60]
Benzodiazepines, oral: Diazepam (*Valium*) Midazolam (*Versed*) Quazepam (*Doral*) Triazolam (*Halcion*)	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]	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.[79]
Budesonide (*Entocort EC*)	Increases oral absorption.[47]	Watch for hypercorticism. Prescribing information advises avoiding grapefruit.[47,78]
Buspirone (*BuSpar*)	Increases absorption and plasma concentrations.[4]	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]
Caffeine	Decreases caffeine clearance.[1]	Watch for possible increase in side effects, such as nervousness or insomnia.
Calcium Channel Blockers: Amlodipine (*Norvasc*) Diltiazem (*Cardizem*) Felodipine (*Plendil*) Nicardipine (*Cardene*) Nifedipine (*Procardia*, *Adalat*) Nimodipine Nisoldipine (*Sular*) Verapamil (*Calan*, *Verelan*, etc)	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.)	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]

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Drug(s)	Findings	Implications*
Carbamazepine (*Tegretol*)	Increases AUC, peak, and trough plasma concentrations.[6]	Look for signs of toxicity, such as dizziness, ataxia, drowsiness, nausea, vomiting, tremor, and agitation.
Carvedilol (*Coreg*)	Increases bioavailability of a single dose by 16%.[14]	The clinical significance of this interaction is not known.
Cilostazol (*Pletal*)	Increases peak.[62]	Clinical significance unknown.
Cisapride (*Propulsid*)	Increases AUC.[36,37]	Contraindicated with grapefruit per U.S. prescribing information.[70]
Clarithromycin (*Biaxin*)	Slightly delays absorption.[59]	Not likely significant.
Clomipramine (*Anafranil*)	Increases plasma concentrations.[15]	Watch for possible increase in side effects, such as dry mouth, somnolence, dizziness, fatigue.
Clozapine (*Clozaril*)	No effect.[49]	None.
Cyclosporine (*Neoral*, *Sandimmune*)	Increases AUC and serum concentrations.[16]	Look for signs of toxicity, such as nephrotoxicity, hepatotoxicity, and increased immunosuppression. Prescribing information advises avoiding grapefruit.[68,78]
Desloratadine (*Clarinex*)	No effect.[49]	None.
Dextromethorphan (e.g., *Robitussin DM*)	AUC increased.[54]	Watch for drowsiness.
Digoxin (*Lanoxin*)	Slight increase in AUC.[48]	Unlikely significant with occasional consumption of a glass of juice.[48]
Erythromycin	Increases AUC and peak.[51]	Theoretical concern for QT prolongation and torsades de pointes.
Estrogens	Increases absorption and plasma concentrations of 17-beta-estradiol and ethinyl estradiol.[17,18]	Effects are unknown at this time.
Etoposide (e.g., *Vepesid*)	Impairs absorption.[49] Mechanism unknown.[83]	Given that this is a chemotherapeutic agent, decreased AUC is concerning.[83] Avoid combination.
Fexofenadine (*Allegra*)	Can decrease AUC by about 40% by inhibiting organic anion transporting polypeptide (OATP).[83,89]	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 (*Clarinex*) as alternative.
Fluvoxamine (*Luvox*)	Peak and AUC increased.[52]	Watch for nausea.

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Drug(s)	Findings	Implications*
HMG-CoA Reductase Inhibitors: Atorvastatin (*Lipitor*) Lovastatin (*Mevacor*) Simvastatin (*Zocor*)	Increases absorption and plasma concentrations by inhibiting gut CYP3A4 metabolism.[20-23,36,37,48]	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.[65,66,78] But other experts suggest avoiding grapefruit with atorvastatin (*Lipitor*), simvastatin, and lovastatin.[48] Consider pravastatin (*Pravachol*) (not affected), rosuvastatin (*Crestor*), or fluvastatin (*Lescol*) as alternatives (not metabolized by CYP3A4).[48]
Haloperidol (*Haldol*)	No significant effect.[49]	None.
Indinavir (*Crixivan*)	Slightly delays absorption.[57,58]	Unknown significance.
Itraconazole (*Sporanox*)	May increase or decrease AUC.[24,84]	The clinical significance of this interaction is unknown.
Levothyroxine	Can decrease AUC by 11% by inhibiting the organic anion transporting polypeptide (OATP).[83]	Separate by four hours.[83]
Losartan (*Cozaar*)	Might reduce the AUC of the major active metabolite.[25]	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.[48]
Methadone (*Dolophine*)	Increases peak and AUC.[53]	Clinically significant effect unlikely, but cannot be ruled out; best to avoid combination.[53]
Methylprednisolone, oral	Increases plasma concentration and half-life of oral methylprednisolone.[26]	Consumption of large amounts of grapefruit might increase the risk of adverse effects.
Montelukast (*Singulair*)	No effect.[85]	None.
Nilotinib (*Tasigna*)	Increases peak by 60% and AUC by 29%.[86]	Prescribing information advises to avoid grapefruit.[87,88]
Omeprazole (*Prilosec*)	No significant effect.[49]	None.
Phenytoin (*Dilantin*)	No effect.[49]	None.
Progesterone (e.g, *Prometrium*)	Increases AUC.[49]	Unknown.
Quinidine	Decreases drug clearance, prolongs the half-life, and delays absorption.[27,56]	The clinical significance of this interaction is unknown.
Quinine	No effect.[49]	None.
Saquinavir (*Fortovase*, *Invirase*)	Increases absorption and plasma concentrations.[28]	Watch for possible increase in side effects, such as fatigue, headache, insomnia, anxiety.
Scopolamine (*Scopace*)	Increases absorption and plasma concentrations.[63]	Unknown.
Sertraline (*Zoloft*)	Increases serum concentrations.[37]	The clinical significance of this interaction is unknown.

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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.[64]	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

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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.[34] Near maximum inhibition of gut CYP3A4 occurs with just 200 mL[48] (less than a typical serving), and even lesser amounts can interact.[49]

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.[76] 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.[48]

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.[42-44] 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.[35]

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.[49] Preliminary research suggests lime juice might also have this effect.[45] 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.[35] There's no proof citrus or grapefruit-flavored sodas interact.[77]

Most adverse events resulting from grapefruit interactions have been minor.[50] However, attempts to classify interactions as "mild," "moderate," or "severe" may be misleading. This is because the

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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.[48] 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].[49] If a patient insists on grapefruit, consider an alternative drug known not to interact.

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Levels of Evidence

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

Level	Definition
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

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

References

1. Fuhr U. Drug Interactions with Grapefruit Juice. *Drug Safety* 1998;(4):251-72.
2. Lilja JJ, Kivisto KT, Backman JT, Neuvonen PJ. Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life. *Eur J Clin Pharmacol* 2000;56:411-5.
3. Ozdemir M, Aktan Y, Boydag BS. Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet* 1998; 23:55-9.
4. Lilja JJ, Kivisto KT, Backman JT, et al. Grapefruit juice substantially increases plasma concentrations of buspirone. *Clin Pharmacol Ther* 1998;64:655-60.
5. Josefsson M, et al. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. *Eur J Clin Pharmacol* 1996;51:189-93.
6. Garg SK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998;64:286-8.
7. Bailey DG, et al. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991;337:268-9.
8. Bailey DG, et al. Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993;54:589-94.
9. Bailey DG, Dresser GK, Kreeft JH, et al. Grapefruit juice-felodipine interaction: Effect of segments and an extract from unprocessed fruit. *Clin Pharmacol Ther* 2000;67(2):107 (abstract PI-71).
10. Uno T, Ohkubo T, Sugawara K, et al. Effects of grapefruit juice on the stereoselective disposition of nicardipine in humans: evidence for dominant presystemic elimination at the gut site. *Eur J Clin Pharmacol* 2000;56:643-9.
11. Grapefruit-drug interactions. URL: powernetdesign.com/grapefruit (Accessed 26 September 1999).
12. Ho PC, Ghose K, Saville D, Wanwimolruk S. Effect of grapefruit juice on pharmacokinetics and pharmacodynamics of verapamil enantiomers in healthy volunteers. *Eur J Clin Pharmacol* 2000;56:693-8.
13. Zaidenstein R, Dishi V, Gips M, et al. The effect of grapefruit juice on the pharmacokinetics of orally administered verapamil. *Eur J Clin Pharmacol* 1998; 54:337-40.
14. *Coreg* monograph. In: Gillis MC, Ed. *Compendium of Pharmaceuticals and Specialities* (CPS). 34th ed. Ottawa, Ontario, CAN: CPhA, 1999:395.
15. Oesterheld J, Kallepalli BR. Grapefruit juice and clomipramine: shifting metabolic ratios. *J Clin Psychopharmacol* 1997;17(1):62-3.
16. Ioannides-Demos LL, et al. Dosing implications of a clinical interaction between grapefruit juice and cyclosporine and metabolite concentrations in patients with autoimmune diseases. *J Rheumatol* 1997;24:49-54.
17. Weber A, et al. Can grapefruit juice influence ethinyl estradiol bioavailability? *Contraception* 1996;53:41-7.
18. Schubert W, et al. Inhibition of 17 beta-estradiol metabolism by grapefruit juice in ovariectomized women. *Maturitas* 1994;20:155-63.
19. Tapaninen T, Neuvonen PJ, Niemi M. Orange and apple juice greatly reduce the plasma concentrations of the OATP2B1 substrate aliskiren. *Br J Clin Pharmacol* 2011;71:718-26.
20. Kantola T, et al. Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998 63:397-402.

More. . .

21. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998 ; 64(5):477-83.
22. Lilja JJ, Kivisto KT, Neuvonen PJ. Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. *Clin Pharmacol Ther* 2000;68:384-90.
23. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999; 66:118-27.
24. Penzak SR, Gubbins PO, Gurley BJ, et al. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. *Ther Drug Monit* 1999;21(3):304-9.
25. Zaidenstein R, Avni B, Dishi V, et al. Effect of grapefruit juice on the pharmacokinetics of losartan in healthy volunteers. *Clin Pharmacol Ther* 1998;65(2): (abstract PI-60).
26. Varis T, Kivisto KT, Neuvonen PJ. Grapefruit juice can increase the plasma concentration of methylprednisolone. *Eur J Clin Pharmacol* 2000;56:489-93.
27. Damkier P, Hansen LL, Brosen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine. *Br J Clin Pharmacol* 1999;48(6):829-38.
28. Kupferschmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. *Br J Clin Pharmacol* 1998;45(4):355-9.
29. Bailey D, Malcolm J, Arnold O, et al. Grapefruit juice-drug interactions. *Br J Clin Pharmacol* 1998;46:101-10.
30. Levien T, Baker D. Selected interactions caused by cytochrome P-450 enzymes. Therapeutic Research Faculty. *Pharmacist's Letter* 1999;15(4):150401.
31. Fuhr U. Drug interactions with grapefruit juice. Extent, probably mechanism and clinical relevance. *Drug Safety* 1998;18:251-72.
32. Fukuda K, Guo L, Ohashi N, et al. Amounts and variation in grapefruit juice of the main components causing grapefruit-drug interaction. *J Chromatog B* 2000;195-203.
33. Takanaga H, Ohnishi A, Murakami H, et al. Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. *Clin Pharmacol Ther* 2000;67:201-14.
34. Lundahl J, Regardh C, Johansson G. The interaction effect of grapefruit juice is maximal after first glass. *Eur J Clin Pharmacol* 1998;54:75-81.
35. Anon. Health Canada Advisory 2002-49, 6/21/02.
36. Greenblatt DJ, Patki KC, von Moltke LL, et al. Drug interactions with grapefruit juice: an update. *J Clin Psychopharmacol* 2001;21(4):357-9.
37. Kane GC, Lipsky JJ. Drug-grapefruit juice interactions. *Mayo Clin Proc*. 2000;75:933-42.
38. Hansten PD, Levy RH. Role of P-glycoprotein and organic anion transporting polypeptides in drug absorption and distribution: focus on H_1 –receptor antagonists. *Clin Drug Invest* 2001;21(8):587-96.
39. Edwards DJ, Fitzsimmons ME, Schuetz EG, et al. 6,7-Dihydroxybergamottin in grapefruit juice and Seville orange juice: effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein. *Clin Pharmacol Ther* 1999;65:237-44.
40. Malhotra S, Bailey DG, Paine MF, et al. Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins. *Clin Pharmacol Ther* 2001;69:14-23.
41. Kehoe WA. Fexofenadine (*Allegra*) and fruit juice. Therapeutic Research Center. *Pharmacist's Letter/Prescriber's Letter* 2001;17(6):170610.
42. Bailey DG, Dresser GK, Kreeft JH, et al. Grapefruit-felodipine interaction: effect of unprocessed fruit and probable active ingredients. *Clin Pharmacol Ther* 2000;68;468-77.
43. Ho PC, Saville DJ, Coville PF, et al. Content of CYP3A4 inhibitors, naringin, naringenin and bergapten in grapefruit and grapefruit juice products. *Pharmaceutica Acta Helvetiae* 2000;74:379-85.
44. Ohtani M, Kawabata S, Kariya S, et al. Effect of grapefruit pulp on the pharmacokinetics of the dihydropyridine calcium antagonists nifedipine and nisoldipine [abstract]. Yakugaku Zasshi 2002 May;122(5):323-9.
45. Bailey DG, Dresser G, Bend J. Lime juice/red wine-felodipine interaction: comparison with grapefruit juice. *Clin Pharmacol Ther* 2002;71(2):P62 [abstract].
46. Product information for *Cordarone*. Wyeth Pharmaceuticals, Inc. Philadelphia, PA 19101. September 2006.
47. Product information for *Entocort EC*. AstraZeneca. Prometheus Laboratories Inc. San Diego, CA 92121. April 2005.
48. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 2004;4:281-97.
49. Saito M, Hirata-Koizumi M, Matsumoto M, et al. Undesirable effects of citrus juice on the pharmacokinetics of drugs: focus on recent studies. *Drug Saf* 2005;28:677-94.
50. Bressler R. Grapefruit juice and drug interactions. Exploring mechanisms of this interaction and potential toxicity for certain drugs. *Geriatrics* 2006;61(11):12-8.
51. Kanazawa S, Ohkubo T, Sugawara K. The effects of grapefruit juice on the pharmacokinetics of erythromycin. *Eur J Clin Pharmacol* 2001;56:799-803.
52. Hori H, Yoshimura R, Ueda N, et al. Grapefruit juice-fluvoxamine interaction-is it risky or not? *J Clin Psychopharmacol* 2003;23:422-4.
53. Benmebarek M, Devaud C, Gex-Fabry M, et al. Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* 2004;76:55-63.
54. Di Marco MP, Edwards DJ, Wainer IW, Ducharme MP. The effect of grapefruit juice and Seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein. *Life Sci* 2002;71:1149-60.

More. . .

55. Yasui N, Kondo T, Furukori H, et al. Effects of repeated ingestion of grapefruit juice on the single and multiple oral-dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology* (Berl) 2000;150:185-90.
56. Min DI, Ku YM, Geraets DR, Lee H. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of quinidine in healthy volunteers. *J Clin Pharmacol* 1996;36:469-76.
57. Penzak SR, Acosta EP, Turner M, et al. Effect of Seville orange juice and grapefruit juice on the indinavir pharmacokinetics. *J Clin Pharmacol* 2002;42:1165-70.
58. Shelton MJ, Wynn HE, Hewitt RG, DiFrancesco R. Effects of grapefruit juice on pharmacokinetic exposure to indinavir in HIV-positive subjects. *J Clin Pharmacol* 2001;41:435-42.
59. Cheng KL, Nafziger AN, Peloquin CA, Amsden GW. Effect of grapefruit juice on clarithromycin pharmacoklinetics. *Antimicrob Agents Chemother* 1998;42:927-9.
60. Demarles D, Gillotin C, Bonaventure-Paci S, et al. Single-dose pharmacokinetics of amprenavir coadministered with grapefruit juice. *Antimicrob Agents Chemother* 2002;46:1589-90.
61. Gupta MC, Garg SK, Badyal D, et al. Effect of grapefruit juice on the pharmacokinetics of theophylline in healthy male volunteers. *Methods Find Exp Clin Pharmacol* 1999;21:679-82.
62. Prescribing information for cilostazol tablets. Andrx Pharmaceuticals, Inc. Ft. Lauderdale, FL 33314. December 2004.
63. Jellin M, Gregory PJ, Batz F, et al. *Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database.* www.naturaldatabase.com (Accessed January 20, 2007).
64. Product information for *Prograf*. Astellas Pharma US, Inc. Deerfield, IL 60015-2548. April 2006.
65. Product information for *Zocor*. Merck & Co., Inc. Whitehouse Station, NJ 08889. August 2005.
66. Product information for *Mevacor*. Merck & Co., Inc. Whitehouse Station, NJ 08889. November 2005.
67. Product information for midazolam syrup. Paddock Laboratories. Minneapolis, MN 55427. March 2004.
68. Product information for *Neoral*. Novartis Pharmaceutical Corporation. East Hanover, NJ 07936. August 2005.
69. Product information for *BusPar*. Bristol-Myers Squibb Company. Princeton, NJ 08543. November 2003.
70. Janssen Pharmaceutics. "Dear Doctor" letter. Important drug warning. January 24, 2000. http://www.fda.gov/medwatch/SAFETY/2000/propul.htm. (Accessed January 23, 2007).
71. Product information for *Ketek*. Aventis Pharmaceuticals, Inc. Kansas City, MO 64137. March 2004.
72. Product information for *Sular*. Shionogi Pharma, Inc. Altanta, GA 30328. February 2010.
73. Product information for *Procardia* capsules. Pfizer, Inc. NY, NY 10017. March 2006.
74. Product information for *Adalat CC*. Bayer Pharmaceuticals Corporation. West Haven, CT 06516. March 2010.
75. *Allegra* product labeling. http://allegra.com/allegra_family.aspx. (Accessed May 12, 2011).
76. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Time course of recovery of cytochrome p450 3A function after single doses of grapefruit juice. *Clin Pharmacol Ther* 2003;74:121-9.
77. Rumor vs Truth. Citrus soft drinks containing grapefruit juice can inhibit the metabolism of some drugs. *Pharmacist's Letter/Prescriber's Letter.* December 8, 2006.
78. Electronic eCPS. Canadian Pharmacists Association. www.e-therapuetics.ca. (Accessed January 25, 2007).
79. Tatro DS, et al. Drug Interactions Facts. Facts and Comparisons 4.0 (online). http://www.efacts online.com. (Accessed January 31, 2007).
80. Product information for *Rapamune.* Wyeth Pharmaceuticals, Inc. Philadelphia, PA 19101. October 2006.
81. Prescribing information for nisoldipine extended-release. Mylan Pharmaceuticals, Inc. Morgantown, WV 26505. January 2010.
82. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2011. Calcium channel blockers monograph (October 2006). http://www.e-therapeutics.ca. (Accessed February 12, 2011).
83. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *Br J Clin Pharmacol* 2010;70:645-55.
84. Greenblatt DJ. Analysis of drug interactions involving fruit beverages and organic anion-transporting polypeptides. *J Clin Pharmacol* 2009;49:1403-7.
85. Mougey EB, Lang JE, Wen X, Lima JJ. Effect of citrus juice and SLC02B1 genotype on pharmacokinetics of montelukast. *J Clin Pharmacol* 2011;51:751-60.
86. Yin OQ, Gallagher N, Li A, et al. Effect of grapefruit juice on the pharmacokinetics of nilotinib in healthy participants. *J Clin Pharmacol* 2010;50:188-94.
87. Product information for *Tasigna*. Novartis. East Hanover, NJ 07936. January 2011.
88. Product monograph for *Tasigna*. Novartis Canada. Dorval, QC H9S 1A9. July 2010.
89. Prescribing information for *Allegra*. Sanofi-Aventis. Bridgewater, NJ 08807. December 2008.

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