

# An overview of interactions between grapefruit juice and drugs

George Muntingh, BPharm, PhD

Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria

**Correspondence to:** Dr George Muntingh, e-mail: george.muntingh@up.ac.za

**Keywords:** grapefruit, furanocoumarin, dihydroxybergamottin, drug interactions, clinical relevance

## Abstract

Because grapefruit contains fibre, vitamin C, antioxidants and phytochemicals, the fruit and its juice are consumed widely to help meet daily nutritional requirements. However, in the past 15 years, studies have shown that grapefruit juice can induce a several-fold increase in the plasma levels of particular drugs that can result in increased therapeutic or even toxic effects. The effect seems to be mediated mainly by inhibition of the cytochrome P450 enzyme CYP3A4 in the wall of the small intestine. This results in a decreased intestinal first-pass metabolism of drugs metabolised by this enzyme leading to higher bioavailability and increased maximum plasma concentrations of the drug. The effect is most pronounced in drugs which experience a high first-pass effect.

The components of grapefruit juice which are the most probable causes of the interaction are the furanocoumarin derivatives. Concomitant grapefruit juice intake does not generally decrease the variability of drug pharmacokinetic parameters. Therefore, it is recommended that patients abstain from drinking grapefruit juice when they are taking a drug that is extensively metabolised, unless a lack of interaction has already been demonstrated for that drug. It is also recommended that drugs possibly interacting with grapefruit juice should be appropriately labelled. The purpose of this article is to examine the cause of this food-drug interaction, discern the list of affected medications and to equip the pharmacist with this knowledge and specify their role in counselling patients on options to avoid the possibility of a grapefruit-drug interaction.

Peer-reviewed. (Submitted: 2011-01-26. Accepted: 2011-07-25.) © Medpharm

S Afr Pharm J 2011;78(8):40-45

## Introduction

The grapefruit (*Citrus paradisi*) derives its common name from the appearance of the fruit growing on the tree in clusters, reminiscent of grapes (Figure 1). Grapefruit were initially thought to have come from the West Indies; Hughes and Browne reported that they were first seen growing in Jamaica and Barbados in the 1600s. However, according to Sinclair, Marloth, who discussed briefly the origin and early distribution of citrus fruits, said some grapefruit trees were growing in South Africa as early as 1661.<sup>1</sup>

Grapefruit are believed to have evolved from the pummelo or pomelo (*C. maxima*), a citrus fruit from the *Rutaceae* (orange) family, through mutation or as a hybrid with the common orange (*C. sinensis*). The grapefruit is larger than an orange but smaller than most pummelos and can yield approximately 160 ml (2/3 cup) of juice. There are seedless and seeded varieties. The flesh comes in three colours, namely white, pink, and ruby red (Figure 2).<sup>2</sup>



Figure 1: Grapefruits growing in a cluster on the tree



**Figure 2:** White, pink and ruby red grapefruit

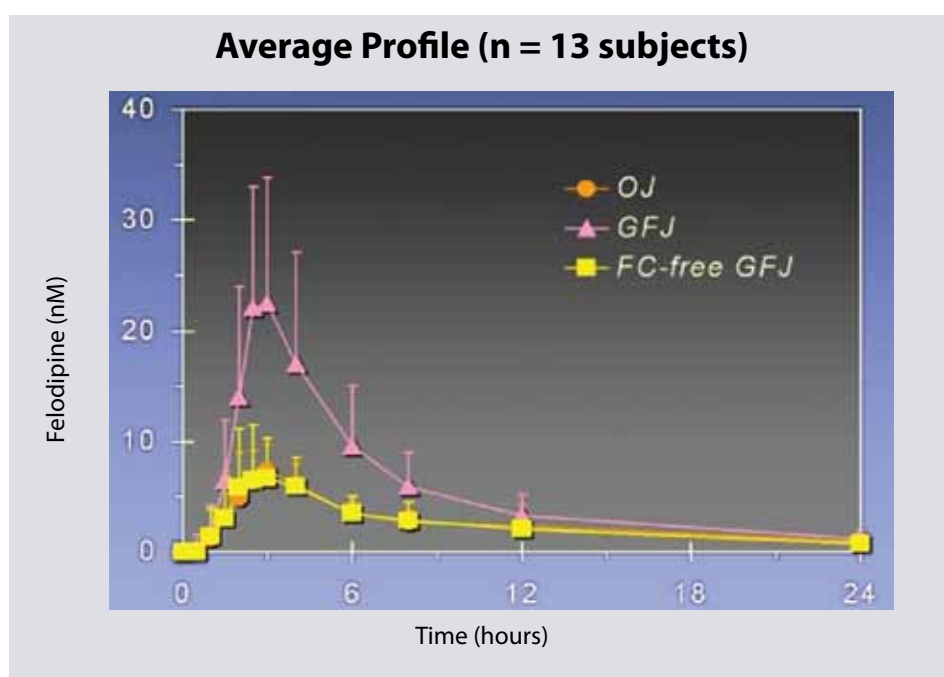
Widely available, grapefruit and grapefruit juice are consumed by many individuals for fibre, vitamin C, antioxidants, and phytochemicals, to help meet daily nutritional requirements. Grapefruit is endorsed by the American Heart Association as a "heart-healthy food" because it contains compounds that may reduce the formation of atherosclerotic plaques.<sup>3,4</sup> It may also inhibit cancer cell proliferation.<sup>5,6</sup>

As many as 15 years ago, investigators found that grapefruit juice can markedly augment oral drug bioavailability. This was an unexpected observation from an interaction study between the dihydropyridine calcium channel antagonist, felodipine, and ethanol, in which grapefruit juice was used as a flavour supplement to mask the taste of the ethanol. A non-intoxicating dose of ethanol or placebo was administered to subjects, followed by 5 mg felodipine. For both study arms, serum felodipine concentrations were noted to be several times greater than that previously reported at the same dose when grapefruit juice was not used (Figure 3).<sup>7</sup> It was recognised

that this finding was possibly due to a pharmacokinetic interaction between grapefruit juice and felodipine.<sup>8</sup> Since this observation, much research has focused on the mechanisms of drug-grapefruit juice interactions and the medications that interact with the juice.<sup>9</sup> Many more drugs have shown enhanced oral bioavailability when consumed with grapefruit juice. Most of the drugs affected by grapefruit juice have poor and highly variable oral bioavailability. In addition, most of these drugs are chiefly metabolised in the body by the cytochrome P450 (CYP) enzyme CYP3A4, found in the liver and intestine.<sup>8</sup>

Grapefruit juice appears to reduce intestinal first-pass metabolism by reducing intestinal CYP3A4 activity, but the effect of co-inhibition of P-glycoprotein is very important and should not be ignored. Because it does not generally affect the systemic clearance of affected drugs, it appears that grapefruit juice selectively reduces intestinal CYP3A4 activity while having little effect on liver CYP3A4.<sup>10</sup> Presumably the active components in grapefruit juice do not reach the liver in sufficient concentrations to affect hepatic CYP3A4 activity, even though a variety of juice components have been implicated in inhibiting these enzymes.<sup>11</sup>

**Figure 3:** The interaction between felodipine and grapefruit juice. Reproduced with permission from the author, Paul B Watkins<sup>7</sup>



OJ = orange juice, GFJ = grapefruit juice, FC = furanocoumarin

### Active components of grapefruit juice

Originally, naringin was thought to be the main component responsible for grapefruit-drug interactions. However, studies have shown naringin to be a weak inhibitor of CYP3A4. It has also been demonstrated that the administration of isolated naringin to humans, in quantities comparable to those found in grapefruit juice, do not cause the same degree of inhibition of intestinal CYP3A4 as grapefruit juice.<sup>10-12</sup>

In addition to flavonoids, researchers have also focused on furanocoumarins found in grapefruit juice as CYP3A4 inhibitors. The furanocoumarins, such

as bergamottin, were originally thought to be responsible for the inhibition of intestinal CYP enzymes.<sup>13</sup> Relative exposures to bergamottin were not known, and doses administered were typically larger than those encountered by humans after normal consumption of grapefruit juice. Thus the relevance of bergamottin in the clinical interaction of grapefruit juice in humans is currently uncertain.<sup>6</sup> The most abundant and probably the single most important furanocoumarin is 6',7'-dihydroxybergamottin (DHB).<sup>13</sup> Reports by different groups indicate that DHB is a potent mechanism-based inactivator or inhibitor of CYP3A4.<sup>10,14</sup> When bergamottin is administered as a pure substance, it enhances the oral bioavailability of some drugs.

However, the effect is much less than that produced by grapefruit juice, even at markedly higher doses of bergamottin than normally present in the juice. Therefore it appears probable that the interaction also involves other furanocoumarins present in whole grapefruit juice. Orange juice has no CYP3A4-inhibiting effects. However, when orange juice was spiked with a synthetic DHB, no significant difference was observed between the degrees of inhibition produced by either orange or grapefruit juice. Therefore, the DHB component in grapefruit appears to be a potent inhibitor of CYP3A4 and is most likely and primarily responsible for the interaction.<sup>15</sup>

The microsomal isoenzyme, CYP3A4, present in the liver and the epithelial cells of the small intestine, accounts for nearly 40% of all CYP isoenzymes (although it is important to note that grapefruit inhibits CYP in the gastrointestinal tract but not in the liver) and is involved in the majority of significant CYP-mediated drug interactions. Inhibition of the CYP3A4 isoenzyme, either reversible or irreversible, will result in a reduced metabolism and metabolic clearance of CYP3A4 substrates.<sup>16</sup>

Although most studies have used fresh grapefruit juice or the reconstituted frozen product, it has been proposed that the substances responsible for drug interactions are also present in the pulp, peel, and core of the fruit.<sup>4</sup> A serious case of rhabdomyolysis in a patient taking the cholesterol-lowering medication simvastatin was believed to be precipitated when the patient began eating a whole grapefruit for breakfast.<sup>17</sup>

### Mechanism of action of grapefruit juice components

DHB and other furanocoumarins appear to reduce mainly intestinal CYP3A4 activity by three related but distinct mechanisms, as follows:<sup>1,13,15,18</sup>

- Competitive or reversible inhibition of CYP3A4.
- Mechanism-based inactivation (also called irreversible inhibition).
- Actual loss of CYP3A4 enzyme.

The first and most common mechanism results from the competition between the inhibitor and substrate for the same CYP isoenzyme required for substrate metabolism and elimination. The effects of competitive inhibition can be observed after administration of the first dose of the inhibitor.

The most potent grapefruit components causing a mechanism-based inactivation of CYP3A4 are furanocoumarins, which bind irreversibly to CYP3A4 and permanently inactivate the isoenzyme. The duration of mechanism-based inhibition may be longer than competitive inhibition because new CYP3A4 isoenzymes must be synthesised for activity to be restored. The onset of the interaction occurs within 30 minutes following intake of a single glass of grapefruit juice with complete recovery of the CYP3A4 taking 48 to 72 hours after the last exposure to grapefruit juice, which explains why the effects may last for at least 72 hours after drinking grapefruit juice.<sup>19</sup> Therefore, it is important to note that, because of mechanism-based inhibition, separating the administration of grapefruit juice and the substrate drug by a few hours does not have a significant ameliorating effect on the grapefruit-drug interaction. Physicians and pharmacists should be aware of this and should advise patients to avoid grapefruit entirely if they are taking medications known to interact significantly with grapefruit juice.

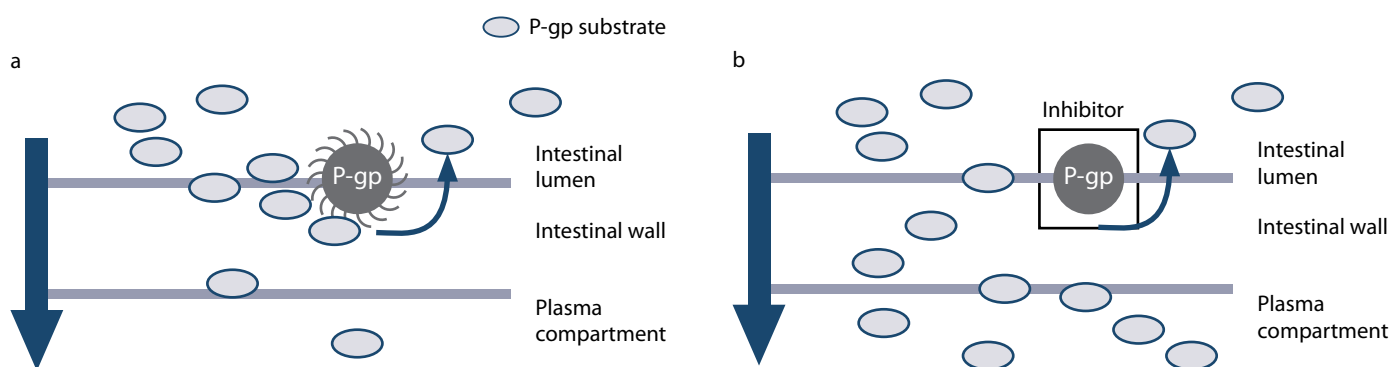
The literature indicates that grapefruit juice has no effect on drug disposition after intravenous administration and does not alter liver CYP3A4 activity. Therefore, this pharmacokinetic interaction is thought to be primarily due to grapefruit juice-mediated inhibition of intestinal CYP3A4 activity, without apparent inhibition of hepatic CYP3A4 activity. Grapefruit juice inhibition of CYP3A4 *in vivo* appears to involve irreversible inactivation of CYP3A4, as evidenced by down-regulation of intestinal CYP3A4 protein content without alteration of intestinal messenger ribonucleic acid levels.<sup>11</sup>

In addition to the effect on intestinal CYP3A4, some evidence suggests that grapefruit juice may also inhibit the drug transporter P-glycoprotein (P-gp), an organic anion transporting peptide.<sup>20-22</sup> P-gp is an efflux membrane transporter (Figure 4).<sup>10</sup> As with CYP3A4, P-gp is found in high concentrations within small intestinal enterocytes, the primary site of oral drug absorption. The role of P-gp is to secrete absorbed drugs actively back into the intestinal lumen. After uptake by the enterocyte, the drugs are either metabolised by CYP3A4 or pumped back out (effluxed) into the lumen by the P-gp transporter. Therefore, simultaneous inhibition of CYP3A4 and P-gp will further increase blood levels of the drug substrate.

### Clinical significance of grapefruit-drug interaction

The clinical significance of grapefruit juice-drug interactions has been debated. Reports of cases of drug toxicity associated with grapefruit juice have been very rare. Although reporting is likely to be incomplete, there are two reasons why the true incidence of clinically significant grapefruit juice-drug interactions is probably low.<sup>23</sup>

Firstly, the drugs affected by grapefruit juice may characteristically have a highly variable apparent oral clearance, probably because of the well-established interpatient variability in activity of intestinal CYP3A4. For this reason, affected drugs must generally have a very wide therapeutic index. (An

**Figure 4:** P-glycoprotein efflux membrane transporter

P-gp = P-glycoprotein

exception is ciclosporin, for which blood level monitoring is generally used to guide individualisation of dosing.)

Secondly, the relative magnitude of response to grapefruit juice for a given patient appears largely to be a function of the patient's relative intestinal CYP3A4 activity. After a standard oral dose of a "susceptible" drug, subjects with a very low CYP3A4 activity in the intestine will tend to have a relatively high area under the curve (AUC). On the other hand, subjects with high intestinal CYP3A4 activity will exhibit a marked increase in AUC when affected drugs are taken with grapefruit juice.

Another situation might arise in a patient with severe liver disease, in whom the intestine is the major site of drug metabolism. Such a patient would be expected to have a high systemic exposure to the drug at usual doses; loss of intestinal CYP3A4 activity would further increase the exposure.

Furthermore, it is possible that certain patients who are particularly predisposed to the toxic effects of a susceptible drug will be more likely to have toxicity when they consume the medicine with grapefruit juice, simply because their systemic exposure to the drug would increase. In the future, as more research data on this interaction become available, it should be possible to use grapefruit-derived furanocoumarins, in a controlled manner, as additives to certain drugs to improve their oral bioavailability, and perhaps through this enable a drug-sparing effect.

Lastly, to assess thoroughly the clinical significance of grapefruit-drug interactions, the amount of grapefruit juice must also be considered. Consumption of a single glass of regular-strength grapefruit juice is sufficient to inhibit CYP3A4.<sup>19</sup> The magnitude of the interaction may vary depending on the extent of intestinal CYP3A4 expression in an individual patient. This variation between individuals may be significant and is difficult to predict. The grapefruit-drug interaction appears to affect patients with high quantities of intestinal CYP3A4 isoenzymes.

Table I gives examples of the effect of grapefruit juice on the oral bioavailability of certain drugs. However, individual variation

among patients and common pharmacological principles should be kept in mind when interpreting this data.

### Reduction in bioavailability of certain drugs by grapefruit juice

When a study was conducted to evaluate the effects of grapefruit juice on the pharmacokinetics of the  $\beta$ -adrenergic receptor-blocking agent celiprolol in healthy volunteers, the results showed that there was a decrease in bioavailability of celiprolol. The grapefruit juice-celiprolol interaction may have been caused by physicochemical factors (e.g. an effect on intraduodenal pH and lipid solubility of celiprolol) or formation of a complex between celiprolol and a component of grapefruit juice. However, other mechanisms, such as inhibition of uptake transporters of the intestine, could also have contributed to the interaction.<sup>18</sup> This suggests that grapefruit may also reduce bioavailability of certain drugs.

### Over-the-counter medications

Research has yet to uncover clinically significant interactions between grapefruit juice and over-the-counter (OTC) medications. However, caffeine, dextromethorphan, chlorpheniramine and loratadine may interact to some degree, but because of the wide therapeutic index of these drugs, occasional use of OTC medications containing these drugs in standard doses with concurrent grapefruit ingestion is not expected to result in significant adverse effects.<sup>18</sup> Caution may be warranted, however, in the elderly and in individuals who may be taking other prescription or non-prescription CYP3A4 inhibitors (e.g. cimetidine, clarithromycin, erythromycin, fluvoxamine, itraconazole, ketoconazole, nefazadone and protease inhibitors). Additionally, dietary supplements or botanical products such as St John's wort may also inhibit CYP3A4, and may result in additive enzyme inhibition with grapefruit.<sup>25</sup>

Table I: Interactions between grapefruit juice and CYP3A4 substrates

Drug class	Significant interaction	Negligible interaction	Findings in significant interaction	Implications of significant interaction
<b>Antiarrhythmics</b>	Amiodarone		Increases <sup>a</sup> AUC by 50% and peak plasma concentration by 84% Pulse rate and QRS intervals are not significantly altered and systolic arterial pressure decreases slightly. <sup>24</sup>	Monitor for arrhythmias and toxicity
	Quinidine		Delays absorption of quinidine and inhibits the metabolism of active metabolite <sup>25</sup>	Clinical significance unknown
<b>Anticonvulsant</b>	Carbamazepine		Increases AUC, peak and trough concentrations by 40% <sup>26</sup>	Monitor for signs of toxicity such as dizziness, ataxia, drowsiness, nausea, vomiting, tremor, and agitation Monitor blood levels
<b>Antidepressants</b>	Sertraline, trazodone, nefazodone, clomipramine		Increased plasma concentration <sup>27</sup>	Monitor for increased side-effects
<b>Antihistamine</b>	Fexofenadine	Desloratadine	May decrease oral absorption and blood levels by inhibiting the organic anion-transporting polypeptide <sup>20</sup>	Clinical significance unknown
<b>Antihypertensives</b>	Carvedilol		Increased bioavailability of a single dose by 16% <sup>28</sup>	Clinical significance is unknown
	Losartan		May reduce the AUC of the major active metabolite <sup>29</sup>	May reduce effectiveness but further studies are needed to determine significance
<b>Anxiolytics and hypnotics</b>	Diazepam, midazolam, triazolam, buspirone	Alprazolam	Increased plasma concentration <sup>30,31</sup>	Monitor for possible increase in sedation
<b>Calcium-channel blockers</b>	Felodipine, nicardipine, nifedipine, nimodipine, isradipine, verapamil	Amlodipine, diltiazem	Increased plasma concentration <sup>32-34</sup>	Monitor for signs of toxicity, e.g. flushing, headache, tachycardia and hypotension
<b>Corticosteroids</b>	Methylprednisolone (oral)	Prednisone	Increased plasma concentration	Consumption of large amounts of grapefruit juice may increase the risk of adverse effects
	Budesonide		Increased oral absorption <sup>35</sup>	Monitor for signs of hypercorticism
<b>Oestrogens</b>	Ethinyl oestradiol		Increased plasma concentration <sup>36</sup>	Clinical significance is unknown
<b><sup>b</sup>HMG-CoA reductase inhibitors</b>	Atorvastatin, lovastatin, simvastatin	Fluvastatin, pravastatin	Increased plasma concentration <sup>29,37,38</sup>	Increased toxicity such as gastrointestinal complaints and muscle pain
<b>Immuno-suppressants</b>	Ciclosporin		Increased plasma concentration <sup>39,40</sup>	Monitor for signs of liver and renal toxicity and side-effects of increased immunosuppression
	Tacrolimus		Possible increased plasma concentration <sup>25</sup>	Monitor for signs of nephrotoxicity and increased immunosuppression
<b>Macrolide antibiotics</b>		Erythromycin	Increased plasma concentration <sup>25</sup>	Clinical significance unknown
<b>Protease inhibitors</b>	Ritonavir, nelfinavir, saquinavir	Indinavir, amprenavir	Increased plasma concentration <sup>12,41</sup>	Monitor for possible increased side-effects
<b>Others</b>	Sildenafil		Increased bioavailability <sup>42</sup>	

a = area under the curve, b = 3-hydroxy-3-methylglutaryl-coenzyme A

## Conclusion: role of the pharmacist

Patients rely on the pharmacist for convenient advice on health issues. Pharmacists, are therefore, well placed to play an important role in minimising potential grapefruit-drug interaction situations. Patients need accurate and specific information. When educating a patient regarding a potential grapefruit-drug interaction, ask about grapefruit or grapefruit juice consumption.

Remember, many fruit juice blends also contain significant amounts of grapefruit juice. Remind patients that most citrus juices, such as sweet orange, lemon, citron and tangerine, are considered safe. However, sour or bitter oranges such as Seville oranges may have an effect similar to grapefruit juice.<sup>18</sup> Lime juice may also interact. In situations where a patient is taking a medication that interacts with grapefruit juice and does not wish to stop consuming it, the pharmacist might suggest other medication options.

Employing their extensive pharmacological background, pharmacists can often predict if a new drug might be a candidate for a significant interaction with grapefruit juice and can do so by considering the following:

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

The following key messages should be conveyed to patients:

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

## References

1. Sinclair WB. The Grapefruit. Its composition, physiology and products. Berkeley: University of California, 1972; p. 1.
2. Kiani J, Imam SZ. Medicinal importance of grapefruit juice and its interaction with various drugs. *Nutr J*. 2007;6:33.
3. Cerda JJ, Robbins FL, Burgin CW, et al. The effects the grapefruit pectin on patients at risk for coronary heart disease without altering diet or lifestyle. *Clin Cardiol*. 1988;11:589-594.
4. Kane GC, Lipsky JJ. Drug-grapefruit interactions. *Mayo Clin Proc*. 2000;75:933-942.
5. Guthrie N, Carroll KK. Inhibition of mammary cancer by citrus flavonoids. *Adv Exp Med Biol*. 1998;439:227-236.
6. Kawaii S, Tomono Y, Katase E, et al. Antiproliferative activity of flavonoids on several cancer cell lines. *Biosci Biotechnol Biochem*. 1999;63:896-899.
7. Paul B Watkins. Grapefruit juice and the intestinal barrier in man: not pulp fiction [homepage on the Internet]. No date [Accessed 2010 Aug 30]. Available from: <http://www.wlap.org/wl-repository/umich/cacr/grand-rounds/20031202-annarbor-01-watkins/real/sld070.htm>
8. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. *Br J Clin Pharmacol*. 1998;46: 101-110.
9. Mertens-Talcott SU, Zadezensky WV, De Castro WV et al. Grapefruit-drug interactions: can interactions with drugs be avoided? *J Clin Pharmacol*. 2006;46:1390-1416.
10. Bailey DG, Kreefk JH, Munoz C, et al. Grapefruit juice-felodipine interaction: effect of naringin and 6,7'-dihydroxybergamottin in humans. *Clin Pharmacol Ther*. 1998;64:248-256.
11. Lundahl J, Regardh CG, Edgar B, et al. Effects of grapefruit juice ingestion: pharmacokinetics and pharmacodynamics of intravenously and orally administered felodipine in healthy men. *Eur J Clin Pharmacol*. 1997;52:139-145.
12. Culm-Merdek KE, von Moltke LL, Gan L, et al. Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: comparison with ritonavir. *Clin Pharmacol Ther*. 2006; 79:243-254.
13. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, et al. Mechanisms of enhanced bioavailability of CYP3A4 substrates by grapefruit constituents: decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. *Drug Metab Dispos*. 1997;25:1228-1233.
14. Edwards DJ, Bernier SM. Naringin and naringenin are not the primary CYP3A inhibitors in grapefruit juice. *Life Sci*. 1996;59:1025-1030.
15. Chan WK, Nguyen LT, Miller VP, Harris RZ. Mechanism-based inactivation of human cytochrome P450 3A4 by grapefruit juice and red wine. *Life Sci*. 1998;62:135-142.
16. Zhang QY, Dunbar D, Ostrowska A, et al. Characterization of human small intestinal cytochromes P-450. *Drug Metab Dispos*. 1999;27:804-809.
17. Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology*. 2004;62:670.
18. Fukuda K, Gua L, Ohashi N, et al. Amounts and variation in grapefruit juice of the main components causing grapefruit-drug interaction. *J Chromatogr*. 2000;741:195-203.
19. Greenblatt DJ, von Moltke LL, Hartz JS, et al. Time course of recovery of cytochrome P450 3A function after single doses of grapefruit juice. *Clin Pharmacol Ther*. 2003;74:121-129.
20. 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.
21. 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;71:1149-1160.
22. Leveille-Webster CR, Arias IM. The biology of the P-glycoproteins. *J Membr Biol*. 1995;143:89-102.
23. Huang SM, Hall SD, Watkins P et al. Drug interactions with herbal products and grapefruit juice: a conference report. *Clin Pharmacol Ther*. 2004;75:1-12.
24. Libersa CC, Brique SA, Motte KB, et al. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol*. 2000;49:373-378.
25. Shimomura S, Wanwimolruk S, Chen JJ. Drug interactions with grapefruit juice: an evidence-based overview. *Pharmacy Times* [homepage on the Internet]. No date [Accessed 2010 Sep 15]. Available from: <https://secure.pharmacytimes.com/lessons/200303-02.asp>
26. Garg SK, Kumar N, Bhargava VK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther*. 1998;64:286-288.
27. Oesterheld J, Kallepalli BR. Grapefruit juice and clomipramine: shifting the metabolic ratios. *J Clin Psychopharmacol*. 1997;17:62-63.
28. Dresser GK, Bailey DG. The effects of fruit juices on drug disposition: a new model for drug interactions. *Eur J Clin Invest*. 2003;2:10-16.
29. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs*. 2004;4:281-297.
30. Kupferschmidt HH, Ha HR, Ziegler WH, et al. Interaction between grapefruit juice and midazolam in humans. *Clin Pharmacol Ther*. 1995;58:20-28.
31. Ozdemir M, Aktan Y, Boydag BS, et al. Interaction between grapefruit juice and diazepam in humans. *Eur J Drug Metab Pharmacokinet*. 1998;23:55-59.
32. Uno T, Ohkudbo T, Sugawara K, et al. Effects of grapefruit juice on the stereoselective disposition of nifedipine in humans: evidence for dominant presystemic elimination at the gut site. *Eur J Clin Pharmacol*. 2000;56:643-649.
33. Fuhr U, Maier-Bruggemann A, Blume H, et al. Grapefruit juice increases oral nifedipine bioavailability. *Int J Clin Pharmacol Ther*. 1998;36:126-132.
34. Pillai U, Muzaffar J, Sen S, Yancey A. Grapefruit juice and verapamil: a toxic cocktail. *South Med J*. 2009;102:308-309.
35. Seidegård J, Randvall G, Nyberg L, Borgå O. Grapefruit juice interaction with oral budesonide: equal effect on immediate-release and delayed-release formulations. *Pharmazie*. 2009;64:461-465.
36. Fingerová H, Oborná I, Petrová P, et al. Does grapefruit juice increase the bioavailability of orally administered sex steroids [article in Czech]? *Ceska Gynekol*. 2003;68:117-121.
37. Lilja JJ, Kivistö KT, Neuvonen PJ. Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther*. 1999;66:118-127.
38. Vaquero MP, Sanchez Muniz FJ, Redondo SJ et al. Major diet-drug interactions affecting the kinetic characteristics and hypolipidaemic properties of statins. *Nutr Hosp*. 2010;25:193-206.
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 Pharm Ther*. 1999;65:237-244.
40. Paine MF, Widmer WW, Pusek SN, et al. Further characterization of a furanocoumarin-free grapefruit juice on drug disposition: studies with cyclosporine. *Am J Clin Nutr*. 2008;87:863-871.
41. Kupferschmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. *Br J Clin Pharmacol*. 1998;45:355-359.
42. Lee M, Min DI. Determination of sildenafil citrate in plasma by high-performance liquid chromatography and a case for the potential interaction of grapefruit juice with sildenafil citrate. *Ther Drug Monit*. 2001;23:21-26.