

Effect of Grapefruit Juice on Bioavailability of Drug.

***Gambhire V. M., Upadhyay N. S., Maheshwari D. N.**

Sinhgad College of Pharmacy, Vadgaon (Bk.), Pune (M.S.), India.

Abstract

Medicines have become an integral part of life for many people. With new medicines and rapidly evolving technologies, accompanied with new drug delivery systems (NDDS), it is becoming more and more convenient to consume drugs. However, new technologies and medicines sometime cause unforeseen side effects with certain foods. Therefore drugs, whether prescription (Rx) or over-the-counter (OTC), need to be taken with caution. Sometimes, certain medications may interact with both the food eaten and the nutrients the food supplies to the body. When the body is unable to use a nutrient due to a drug that has been taken, nutrient-drug interaction occurs. Food-drug interactions may impact the body in several ways. Certain foods can affect the rate at which the body uses a medication. The effectiveness of a drug is also altered if a certain nutrient in a food speeds up or slows down metabolism. Elaborating on this it can be said that foods impact the availability of the drug and the profile of its concentration in the blood, depending on the nature of the food, time at which it is taken, gap between the time of consumption of food and drug.

Key Words

Grapefruit, drug interactions, bergamottin, 6, 7- dihydroxybergamottin, CYP3A4 inhibition.

Introduction

When food and drug is taken together the component of food and drug interacts with each other and affect the availability of drug. It is best to have a diet high in fats when drugs like Griseofulvin (an antifungal) are to be taken to improve their absorption. Simple things like tea, coffee, and several fruit juices have been known to cause changes in drug availability. Taking the same drug with hot or cold water also makes a difference. Food or juice affects the bioavailability of certain medications by inhibiting certain intestinal enzymes such as CYP3A4 as well as P-glycoprotein and Organic Anion Transporting Polypeptide (OATP) transporters. A medication has ingredients, just as food does, that allows it to function correctly when taken in order to help the body in some way. Food can interfere with the effectiveness of a drug if it interacts with the ingredients in the medicine, preventing the drug from working properly. Nutrients in food may either delay absorption into the body, speed up elimination from the body, or can impact a drug's effectiveness. For example, the acidic ingredients in fruit juices are capable of decreasing the power of antibiotics, such as penicillin.

Tetracycline, another infection-fighting drug, is impacted by the consumption of dairy products. Grapefruit juice may react with several medications, which will lead to an increase in systemic exposure. Apart from this, anti depressants can also be dangerous if mixed with beverages or foods that contain tyramine, which is found in items such as beer, red wine, and some cheeses. Grapefruit is a subtropical citrus tree known for its bitter fruit¹. These evergreen trees are usually found at around 5–6 meters (16–20 ft) tall, although they can reach 13-15 meters. The leaves are dark green, long and thin. It produces 5 cm white four petaled flowers. The fruit is yellow-orange skinned and largely oblate and ranges in diameter of 10-15 cm. the flesh is segmented and acidic, varying in color, depending on cultivars, which include white, pink, and red pulp of varying sweetness.² Grapefruit is a good source of many nutrients and phytochemical that contributes to a healthy diet. Grapefruit contains vitamin C, lycopenes, antioxidants, and pectin fiber. Studies have shown that the grapefruit helps lowers cholesterol and seeds have a high content of antioxidant properties.^{3, 4, 5, 6, 7, 8.}

Grapefruit Juice and its Interaction

Grapefruit and grapefruit juice have the potential to interact with numerous drugs. A number of organic compounds, identified as furanocoumarin derivatives,

***Corresponding Author:**

vaishaligambhire@gmail.com

interfere with the intestinal enzyme cytochrome P450 isoform CYP3A4 and are therefore primarily responsible for the interaction. However, bioactive compounds in grapefruit juice may also interfere with P-glycoprotein and organic anion transporting polypeptides (OATPs) either increasing or decreasing bioavailability a number of drugs. In 1989 a pharmacological study evaluated the possibility of an interaction between ethanol ingestion and medication with the dihydropyridine calcium channel blocker - felodipine. Grapefruit juice was used as a flavoring additive during the test. The results of study showed several-fold increase of felodipine concentrations compared to results obtained in other investigations of the drug. Additionally, there were lower blood pressure readings and more adverse effects compared to the group of subjects on felodipine alone. Further investigations revealed that grapefruit juice strikingly elevated felodipine bioavailability and could influence its other pharmacokinetic and pharmacodynamic properties.⁹ Grape fruit juice can have a number of interaction with drugs often increasing the effective potency of compound. Grapefruit contains naringin, bergamottin and dihydroxybergamottin, which inhibit the protein isoform CYP3A4 predominately in the small intestine, but at higher doses, hepatic CYP3A4 inhibition is present as well.¹⁰ It is via inhibition of this enzyme that grapefruit increases the effects of a variety of drugs by increasing their bioavailability.^{11,12, 13, 14, 15, 16} The effect of grapefruit juice with regard to drug absorption was originally discovered in 1989. However, the effect became well-publicized after being responsible for a number of deaths due to overdosing on medication.¹⁷ Grapefruit juice may be the first documented, but apple and orange juices have been also implicated in interfering with etoposide, a chemotherapy drug, some beta blocker drugs used to treat high blood pressure, and cyclosporine, taken by transplant patients to prevent rejection of their new organs.¹⁸

Active component of Grape fruit 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 was also demonstrated that the administration of isolated naringin to humans, in quantities comparable to those found in grapefruit juice, did not cause the

same degree of inhibition as grapefruit juice.^{19, 20, 21.} The assumption is that the active components in grapefruit juice do not reach the liver in sufficient concentrations to affect CYP3A4 activity; although a variety of juice components have been implicated to inhibit this enzymes.^{22, 23} In addition to flavonoids, researchers have also focused on furanocoumarins found in grapefruit juice as CYP3A4 inhibitors. The furanocoumarins such as bergamottin was mainly thought to be responsible for the inhibition of intestinal CYP enzymes.^{24, 25} Bergamottin is present in grapefruit juice in concentrations ranging from 2 to 30 $\mu\text{mol/L}$. Relative exposure to bergamottin is 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.²⁶ But, the most abundant and probably the most important single furanocoumarin is 6, 7-dihydroxybergamottin (DHB)^{19,27,28}. When bergamottin administered as a pure substance enhanced the oral bioavailability of some drugs. However, the effect was substantially less than that produced by grapefruit juice even at markedly higher doses of bergamottin than normally present in the juice. It appears probable that the interaction also involves other furanocoumarins present in whole grapefruit juice, possibly acting in combination by additive or synergistic mechanisms. Bergamottin has systemic availability and is metabolized to 6', 7'-dihydroxybergamottin in humans²⁸. The more hydrophilic metabolite, 6', 7'-dihydroxybergamottin, is often present in grapefruit juice in similar concentrations (0.8 to 58 $\mu\text{mol/L}$), but initial investigations indicated that it is a less potent with respect to in vitro mechanism-based inactivator of CYP3A4 than bergamottin.²⁶ However, recent reports by different groups indicate that 6',7'-dihydroxybergamottin is a more potent mechanism-based inactivator or inhibitor of CYP3A4. The interaction between grapefruit juice serum and felodipine can be attributed largely to DHB. This establishes DHB as an important contributor to the grapefruit juice effect. These novel findings indicate that DHB could account almost entirely for the effect of the aqueous extract of grapefruit juice on the systemic exposure of felodipine, supporting a major role for DHB in the grapefruit juice effect.²⁸

Orange juice has no CYP3A4-inhibiting effects. When orange juice was spiked with a synthetic DHB, however, no significant difference between the degrees of inhibition produced by either of the 2 citrus fruits was observed. Therefore, the DHB component in grapefruit appears to be another potent inhibitor of CYP3A4 and is most likely primarily responsible for the interaction. The furanocoumarins are divided into 6 components: 6',7'-dihydroxybergamottin (DHB), GF-I-1, bergamottin (GF-I-2), GF-I-4, GF-I-5 (bergamottin-6',7'-epoxide), and GFI- 6.12 Significant inhibition of CYP3A4 isoenzyme activity is exhibited by DHB, GF-I-1, and GF-I-4 with minimal activity exhibited by bergamottin (a presumed precursor of GF-I-1 and GF-I-4 and a known ingredient of grapefruit essential oil)²⁹. The CYP3A4 isoenzyme, which is found in the intestine and liver, accounts for about 40% to 60% of all CYP450 isoenzymes (although it is important to note that grapefruit inhibits CYP450 in the gastrointestinal tract, not the liver) and is involved in the majority of significant CYP450-mediated drug interactions. Inhibition of the CYP3A4 isoenzyme, either reversible or irreversible, will result in a reduced metabolism and metabolic clearance of CYP3A4 substrates²³. Some of the components of grapefruit such as Paradisin C have also shown CYP3A4 isoenzyme inhibitory activity. Paradisin C was isolated from the grapefruit and the activity was reported as against Paradisin A and B.³⁰ Other reported components are β -citraurin, D-limonene, myrcene, sabinene³¹ and limonoids. Grapefruit contains many flavonoid glycosides, naringenin, quercetin, kaempferol, hesperetin and apigenin being the most abundant among their aglycones.^{32, 33, 34}

Mechanism of Action of Grapefruit Juice

There are basically three mechanisms by which grapefruit juice acts:

1) Competitive or Reversible Inhibition: The first and most common mechanism is known as competitive inhibition and 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.

(2) Mechanism-Based Inactivation (Also Called Irreversible Inhibition): The second mechanism is

known as mechanism-based inhibition and occurs with grapefruit juice. 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 synthesized for activity to be restored. Complete recovery of the CYP3A4 may take 48 to 72 hours after the last exposure to grapefruit juice, which explains why the effects can last for at least 72 hours after drinking grapefruit juice. Literature indicated that grapefruit juice at normal volume did not change the terminal half-life ($t_{1/2}$) or intravenous pharmacokinetics of drugs. 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.

(3) Actual Loss of Cyp3a4 Enzyme: The latter mechanism was first noticed when small intestinal biopsy specimens were obtained in healthy volunteers before and after drinking grapefruit juice. With the use of antibodies specific for CYP3A4, it was noted that the intestinal content of CYP3A4 fell by more than 50% after consumption of even a single glass of grapefruit juice. It was then noted that this phenomenon could be reproduced with grapefruit extract or purified DHB in a human intestinal cell line (Caco2) modified to express CYP3A4. Studies performed in these cells have indicated that loss of CYP3A4 in response to DHB exposure is exclusively caused by accelerated degradation of CYP3A4. This is consistent with the observation in humans that grapefruit juice-mediated loss of CYP3A4 protein is not associated with a reduction in CYP3A4 messenger ribonucleic acid. The effect of grapefruit juice is mainly by inhibiting the first metabolism. In intestine the amount of the enzyme is more hence the effect is more on intestine, while in liver the amount is less hence the effect is less in liver and there is no enzyme in blood hence when drug is given intravenously there is no effect.

In addition to the effect on CYP3A4, grapefruit juice may also inhibit the drug transporters P-glycoprotein (P-gp) and organic anion transporting peptide (OATP).³⁶ P-gp is an efflux membrane transporter pump belonging to the adenosine triphosphate-binding cassette family of proteins. As with CYP3A4, P-gp is found in high concentrations within intestinal enterocytes, the primary site of oral drug absorption. The role of P-gp is to actively secrete absorbed drugs back into the intestinal lumen. After uptake by the enterocyte, the drugs are either metabolized by CYP3A4 or pumped back out (effluxed) into the lumen by the P-gp transporter. Therefore, inhibition of CYP3A4 or P-gp will increase blood levels of the drug substrate. Some evidence suggests that active grapefruit components may inhibit intestinal P-gp¹⁵. The CYP3A4 isoform of cytochrome P450 is located in both the liver and the enterocytes. Many oral drugs undergo first-pass (presystemic) metabolism by the enzyme. Several organic compounds found in grapefruit and specifically in grapefruit juice exert inhibitory action on drug metabolism by the enzyme. It has been established that a group of compounds called furanocoumarins are responsible for this interaction and not flavonoid as was previously reported.¹⁶ The list of active furanocoumarins found in grapefruit juice includes: bergamottin, bergapten, bergaptol and 6',7'-dihydroxybergamottin. Another mechanism of interaction is possibly through the P-glycoprotein (Pgp) that is localized in the apical brush border of the enterocytes. Pgp transports lipophilic molecules out of the enterocyte back into the intestinal lumen. Drugs that possess lipophilic properties are either metabolized by CYP3A4 or removed into the intestine by the Pgp transporter. Both the Pgp and CYP3A4 may act synergistically as a barrier to many orally administered drugs. Therefore their inhibition (both or alone) can markedly increase the bioavailability of a drug. The interaction caused by grapefruit compounds lasts for up to 24 hours and its effect is the greatest when the juice is ingested with the drug or up to 4 hours before the drug¹⁷. The flavonoid existing in highest concentration in grapefruit juice is naringin, which in humans is metabolized to naringenin. Other flavonoids exist in grapefruit juice in lower concentrations as well. Orange juice does not contain naringin in as high a concentration, instead containing hesperetin. It is sometimes recommended as a substitute. Juice of

limes and Seville oranges can also inhibit drug metabolism, however, as can apple juice with some drugs.

Onset, duration and magnitude of effect of Grapefruit Juice on inhibition of CYP3A4 enzymes:

Furanocoumarins are found predominantly in the grapefruit flesh followed by the sac, peel, and seed. The onset of the interaction can occur within 30 minutes following intake of a single glass of grapefruit juice, and the inhibition can last up to 3 days following the last administration of grapefruit juice. Concomitant intake of high amounts of grapefruit juice and the CYP3A4 substrate simvastatin increased the C_{max} and AUC(0-∞) of simvastatin and simvastatin acid about 5- to 15-fold. When simvastatin is taken 24 hours after ingestion of grapefruit juice, the extent of the interaction is about 90% smaller than during concomitant administration of simvastatin and grapefruit juice. The interaction potential of even high amounts of grapefruit juice with CYP3A4 substrates dissipates within 3 to 7 days after the last dose of grapefruit juice.¹⁷

Clinical significance of Grapefruit 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 incomplete, there are two reasons why the true incidence of clinically significant grapefruit juice–drug interactions is probably low. Firstly, the drugs affected by grapefruit juice characteristically have highly variable apparent oral clearance, presumably because of well-established inter-patient variability in activity of intestinal CYP3A4. For this reason, affected drugs must generally have a very wide therapeutic index (an exception is cyclosporine, for which blood level monitoring is generally used to guide individualization of dosing). Secondly, the relative magnitude of response to grapefruit juice for a given patient appears to largely be a function of his or her relative intestinal CYP3A4 activity. After a standard oral dose of a “susceptible” drug, subjects with very low CYP3A4 activity in the intestine will tend to have a relatively high AUC. Grapefruit juice should have a relatively small effect on pharmacokinetics in these individuals because there is little intestinal CYP3A4 activity to inhibit. In contrast, subjects with high intestinal CYP3A4 activity will have a marked increase in AUC when

affected drugs are taken with grapefruit juice. A situation in which toxicity could occur would be in patients who have been given higher than usual doses of a susceptible drug and then begin drinking grapefruit juice for the first time. This could occur if the physician increases the drug dose to a desired pharmacologic effect. The dose in a patient with very high intestinal CYP3A4 activity might then be titrated to an unusually high daily dose of drug. A sudden fall in intestinal CYP3A4 activity, as would occur after drinking grapefruit juice, could then result in drug toxicity. Finally to thoroughly assess the clinical significance of grapefruit-drug interactions, the type and amount of grapefruit juice must also be considered. Consumption of a single glass of regular-strength grapefruit juice is sufficient to inhibit CYP3A4. The magnitude of 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 small bowel CYP3A4 isoenzymes.

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 β -adrenergic receptor–blocking agent celiprolol in healthy volunteers the results showed that there was 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.¹⁸ This suggests that grapefruit may also affect in reduction in bioavailability of certain drugs.

Responsibility of the pharmacist to bring this issue to public attention

As a widely available fruit source to help meet daily nutritional requirements, grapefruit and grapefruit juice are consumed by many individuals for the fiber, vitamin C, antioxidants, and phytochemicals. For this reason, pharmacists need to understand grapefruit drug interactions as well as common public misinformation, and communicate any potential interaction risks to patients.

The following key messages should be communicated 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.
- The effects of OTC products and herbal medications, although believed to be safe based on the current literature, 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.

The following drugs definitely interact with CYP3A4:

Bupropion, amfebutamone, Wellbutrin (Welbutrin), Paroxetine, paroxetine hydrochloride, Valproate semisodium, divalproex sodium, carbamazepine¹⁹, digoxin,²⁰ buspirone,²¹ Benzodiazepines, including: alprazolam, diazepam, midazolam, lorazepam, oxazepam, and chlordiazepoxide.

Additional drugs found to be affected by grapefruit juice include

Statins such as atorvastatin,²² lovastatin,^{23, 24} and simvastatin, Dihydropyridines²⁵ including felodipine (Plendil), nifedipine, diltiazem, nisoldipine, nitrendipine, losartan, repaglinide, verapamil, Antiarrhythmics including amiodarone, quinidine, Cardioquin, disopyramine, propafenone, and carvediol. The male impotence drugs sildenafil (Viagra), tadalafil and vardenafil. The anti-migraine drugs ergotamine and nimodipine

Probably Non-Interacting drugs

The following drugs, at least when not interacting with other drugs, are probably safe when consumed with grapefruits: Lamotrigine, Lamictal.

Conclusion

Firstly when considering how to manage grapefruit drug interactions, a pharmacist should be competent enough to decide whether the interaction is clinically relevant. A number of medications are reported to have interactions with grapefruit. However many of the other medications have not been proven clinically significant to have interaction. The importance of clearly understanding possible interactions with grapefruit products is becoming more evident.

Secondly, when thinking of substitute for grapefruit juice, there are several other fruit juices available including orange juice as a first choice. Orange juice does not contain responsible components in high concentration, instead containing hesperetin, and may be recommended as a substitute for grapefruit. Lastly in the recent studies on recovery of the intestinal CYP3A4 enzymes after consuming grapefruit juice suggest that during the clinical trials

and pharmacokinetic studies, grapefruit juice should be avoided at least for 72 hours rather than 48 hours or less so that possible inter-subject variability in pharmacokinetic parameters can be reduced. In addition, it is recommended that drugs possibly interacting with grapefruit juice should be appropriately labeled and more studies are needed to clarify interactions involving OTC medications and herbal medications.

Table 1: Interaction between Grape fruit Juice and some drugs.

Drug	Possible adverse event	Clinical importance	Extent of evidence	Severity / Onset
Amiodarone	Reduction in major metabolite production and increase in serum amiodarone concentration	May be clinically significant	poor	Major/ Delayed
Amlodipine	Increased serum amlodipine concentrations. No adverse haemodynamic effects reported.	Unlikely to be clinically significant	Poor	Minor/ Delayed
Atorvastatin	Increased bioavailability of atorvastatin resulting in increased risk of myopathy or rhabdomyolysis	May be clinically significant	Fair	Moderate/ Rapid
Benzodiazepines	No data exists but theoretically none	Unlikely to be clinically significant	None	None/ Unknown
Buspirone	Elevated plasma concentrations resulting in increased risk of adverse effects	Clinical significance unknown - there is considerable inter-individual variability with serum levels	Poor	Minor/ Delayed
Carbamazepine	Increased carbamazepine bioavailability	May be clinically significant	Fair	Moderate/Rapid
Cisapride	Increasing serum concentrations increase the risk of adverse effects (e.g. cardiotoxicity, QT prolongation, torsade de pointes)	Experimental data are fair but clinical significance unknown. Monitor for adverse effects or avoid grapefruit juice	Fair	Major/ Rapid
Clarithromycin	No increase in drug concentrations noted	Insignificant	Poor	None/ Not specified
Clomipramine	Increased risk of clomipramine toxicity	Clinical significance unknown. Monitor for adverse effects.	Poor	Moderate/Delayed
Corticosteroids	None	Insignificant	Poor	None/ Not specified
Cyclosporin	Increased risk of cyclosporin toxicity (e.g. renal dysfunction, cholestasis, paraesthesia)	Clinically significant interaction	Good	Moderate/Delayed
Diazepam	Increased plasma concentrations of diazepam	Unlikely to be clinically significant	Poor	Moderate/Rapid
Digoxin	No adverse reports found	Unlikely significant	Theoretical	Not specified
Diltiazem	None	Insignificant	Poor	None/ Not specified

Felodipine	Increased serum concentrations result in increased risk of adverse effects (e.g. severe hypotension, myocardial ischaemia)	May be clinically significant	Good	Moderate/Rapid
Fexofenadine	No adverse reports found	Clinical significance unknown	Theoretical	Unknown/Rapid
Fluvastatin	None	Unlikely to be clinically significant	Poor	None/ Not specified
Haloperidol	None	Insignificant	Poor	None/ Not specified
Indinavir	None	Insignificant	Fair	None/ Not specified
Itraconazole	Decreased oral bioavailability possible, resulting in an increased risk of antifungal failure	Clinical significance unknown, therefore monitor patients for altered response	Fair	Moderate/Rapid
Loratadine	Increased serum concentrations possible, may increase the risk of adverse effects	Unlikely to be clinically significant	Theoretical	Unknown/Rapid
Methadone	Increased serum concentrations may increase the risk of adverse effects	Clinical significance unknown	Theoretical	Unknown/Rapid
Methylprednisolone	Increased plasma concentrations of methylprednisolone but no significant change in plasma cortisol levels	Clinical significance of this interaction for most patients is likely to be small	Poor	Moderate/Rapid
Midazolam	Increased bioavailability and pharmacodynamic effects of midazolam	Little clinical significance	Fair	Moderate/Rapid
Nicardipine Nifedipine	Increased serum concentrations increasing the risk of adverse effects, however no adverse haemodynamic effects reported	Insignificant	Good	Moderate/Rapid
Nimodipine	Increased nimodipine bioavailability. No adverse haemodynamic effects reported.	Unlikely to be clinically significant	Poor	Moderate/Rapid
Omeprazole	None	Insignificant	Poor	Moderate/Rapid
Pimozide	Possible increased serum concentrations	Theoretical. Unlikely to be clinically significant	Poor	Major/ Rapid
Pravastatin	None	Insignificant	Poor	None/ Not specified
Prednisolone	None	Insignificant	Poor	None/ Not specified
Quinidine	Decreased metabolic conversion of quinidine to its major metabolite. Neither quinidine toxicity nor prolonged haemodynamic changes were observed.	Unlikely to be clinically significant	Fair	Minor/ Rapid
Quinine	None reported	Insignificant (its metabolism is predominantly hepatic rather than intestinal therefore grapefruit juice has a minimal effect)	Poor	None/ Not specified
Saquinavir	Grapefruit juice increases the bioavailability of oral (not intravenous) saquinavir significantly	Clinical significance unknown as there is a high inter-individual variability in the bioavailability of saquinavir. Monitor patients for altered response.	Poor	Minor/ Rapid
Sertraline	Grapefruit juice may inhibit the metabolism of sertraline elevating serum concentrations	Clinical significance unknown. No increase in adverse effects	Poor	Moderate/Delayed

		reported. Monitor patients for altered response.		
Simvastatin	Increased serum simvastatin concentrations resulting in increased adverse effects (e.g. myopathy, rhabdomyolysis)	May be clinically significant	Fair	Moderate/Rapid
Sirolimus	Increased plasma concentrations resulting in an increased risk of toxicity	May be clinically significant	Fair	Moderate/Delayed
Tacrolimus	Significantly increased plasma concentrations and increased risk of toxicity	May be clinically significant	Poor	Moderate/Delayed
Theophylline	None	Insignificant	Poor	None/ Not specified
Triazolam	Increased serum triazolam concentrations resulting in increased sedation	Unlikely to be clinically significant	Fair	Minor/ Rapid
Verapamil	None	Insignificant	Poor	None/ Not specified
Warfarin	None	Insignificant	Poor	None/ Not specified

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