Interactions between grapefruit juice and some drugs available in Australia

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NOTES

- Drugs which are not available in Australia at the time of publication are not listed.
- The absence of a drug from this table does not indicate that there is no interaction.

Drug	*Possible adverse event*	*Clinical importance*	*Extent of evidence*	*Severity/ Onset*	*Summary of study data*
Amiodarone	Reduction in major metabolite production and increase in serum amiodarone concentration	**May be clinically significant**	Poor	Major/Delayed	A study of 11 healthy volunteers showed that grapefruit juice inhibited the production of N-desmethylamiodarone (the major metabolite of amiodarone) and significantly increased the AUC* and Cmax† of amiodarone. The reductions in PR and QT_c intervals caused by amiodarone were also diminished.[1]
Amlodipine	Increased serum amlodipine concentrations. No adverse haemodynamic effects reported.	**Unlikely to be clinically significant**	Poor	Minor/Delayed	A controlled study found a slight interaction between amlodipine and grapefruit juice, the amlodipine AUC was 116% and Cmax was 115% of normal values. There were no differences in blood pressure and heart rate.[2]
Atorvastatin	Increased bioavailability of atorvastatin resulting in increased risk of myopathy or rhabdomyolysis	**May be clinically significant**	Fair	Moderate/Rapid	Grapefruit juice was found to increase the AUC of atorvastatin acid and atorvastatin lactone approximately threefold. AUC of active and total atorvastatin increased by 20–50%.[3]
Benzodiazepines (see also diazepam and triazolam)	No data exists but theoretically none	**Unlikely to be clinically significant**	None	None/Unknown	No data exist for alprazolam, chlordiazepoxide, clonazepam, flurazepam and lorazepam. However, they are all likely to be safe to take with grapefruit juice as their high oral bioavailability leaves little room for elevation by grapefruit juice.[4]
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	A study of 10 healthy volunteers found that 200 mL of double strength grapefruit juice three times a day increased buspirone's AUC, peak concentration, time to peak concentration and half-life. However, there was considerable inter-individual variability.[5]
Carbamazepine	Increased carbamazepine bioavailability	**May be clinically significant**	Fair	Moderate/Rapid	Grapefruit juice increased peak concentration by 40.4%, trough concentration by 39.2% and AUC by 40.8% during a randomised crossover study.[6]
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	Grapefruit juice was shown to increase the oral bioavailability of cisapride in 14 volunteers but large inter-individual variations were noted. There was a **slight** but significant increase in the elimination half-life of cisapride during a two-phase crossover study. No volunteer experienced a change in heart rate, blood pressure or QT interval.[7,8]

Drug	*Possible adverse event*	*Clinical importance*	*Extent of evidence*	*Severity/ Onset*	*Summary of study data*
Clarithromycin	No increase in drug concentrations noted	**Insignificant**	Poor	None/Not specified	A randomised crossover study of 12 healthy volunteers showed that grapefruit juice increased time to peak concentration but did not affect other pharmacokinetic parameters.[9]
Clomipramine	Increased risk of clomipramine toxicity	**Clinical significance unknown. Monitor for adverse effects.**	Poor	Moderate/Delayed	Clomipramine is metabolised by several different CYP pathways including 1A2, 3A4 and 2D6. Grapefruit juice inhibits 3A4. Two case reports showed that grapefruit juice increased the trough plasma concentration of clomipramine. Whether this inhibition is sustained over time is not known. The increase could be due to effects on the intestinal rather than hepatic CYP3A4.[10]
Clozapine	None	**Insignificant**	Poor	None/Not specified	One study showed no interaction with clozapine or its major metabolite desmethylclozapine.[11]
Contraceptives – oral	None	**Unlikely to be clinically significant**	Poor	None/Not specified	There is an increase in AUC of 28% and serum concentrations of 37% when 50 microgram of ethinyloestradiol is taken with 200 mL of grapefruit juice. It seems unlikely that this interaction is of practical importance as the increased bioavailability is still less than the extent of known variability between individuals. Similar results have been seen with oestradiol and oestrone.[4]
Corticosteroids	None	**Insignificant**	Poor	None/Not specified	Grapefruit juice had no significant effect on the AUC of prednisolone or prednisone.[12]
Cyclosporin	Increased risk of cyclosporin toxicity (e.g. renal dysfunction, cholestasis, paraesthesia)	**Clinically significant interaction**	Good	Moderate/Delayed	Cyclosporin and cyclosporin metabolite serum concentrations may be significantly increased when this drug is co-administered with grapefruit juice. In one study exposure to grapefruit juice increased the mean AUC by 50% for cyclosporin and 236% for cyclosporin metabolites. The magnitude of the effect is variable among patients and the consistency of the interaction with repeat dosing has not been documented. Therefore concurrent administration is not recommended.[10,13]
Diazepam	Increased plasma concentrations of diazepam	**Unlikely to be clinically significant**	Poor	Moderate/Rapid	A study of eight healthy volunteers given 5 mg diazepam and 250 mL of grapefruit juice showed an increase in peak concentrations of 1.5 times and an increase in time to peak concentration from 1.5 hours to 2.06 hours.[4,14]
Digoxin	No adverse reports found	**Unlikely to be clinically significant**	Theoretical	Unknown/ Not specified	Theoretical interaction based upon the knowledge that digoxin is a Pgp substrate. However, the effect of grapefruit juice on Pgp is unclear and the *in vivo* impact of grapefruit juice on medicines which are solely substrates of Pgp, such as digoxin, is still to be determined. No clinical studies found.[15]
Diltiazem	None	**Insignificant**	Poor	None/Not specified	Bioavailability of diltiazem is unaltered by grapefruit juice.[13]
Felodipine	Increased serum concentrations result in increased risk of adverse effects (e.g. severe hypotension, myocardial ischaemia)	**May be clinically significant**	Good	Moderate/Rapid	Bioavailability of felodipine when taken with grapefruit juice can be 2–3 times greater than when taken with water. The haemodynamic effects of felodipine (lowered diastolic pressure, increased heart rate) are approximately doubled as are vasodilator adverse effects. The magnitude of the interaction is highly variable among individuals. However, many studies have shown enhanced blood pressure reduction, an increase in heart rate and an increase in vasodilatory adverse effects when felodipine is taken with grapefruit juice. It has been suggested that grapefruit juice should be stopped 2–3 days before administration of felodipine to prevent the interaction.[10,13,16,17]

Drug	*Possible adverse event*	*Clinical importance*	*Extent of evidence*	*Severity/ Onset*	*Summary of study data*
Fexofenadine	No adverse reports found	**Clinical significance unknown**	Theoretical	Unknown/Rapid	Theoretical interaction based upon the knowledge that fexofenadine is a Pgp substrate. However, the effect of grapefruit juice on Pgp is unclear and the *in vivo* impact of grapefruit juice on medicines which are solely substrates of Pgp is still to be determined. No clinical studies found.[15]
Fluvastatin	None	**Unlikely to be clinically significant**	Poor	None/Not specified	CYP3A4 plays only a minor role in the metabolism of fluvastatin and is therefore unlikely to be affected by grapefruit juice.[10,18]
Haloperidol	None	**Insignificant**	Poor	None/Not specified	No interaction was found in 12 schizophrenic patients previously stabilised on haloperidol. There was also no change in the clinical status of the patients during grapefruit juice administration.[13]
Indinavir	None	**Insignificant**	Fair	None/Not specified	A single 400 mg indinavir dose with 240 mL of grapefruit juice resulted in a 26% decrease in the AUC of indinavir. Manufacturer does not recommend dosage changes.[13]
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	A study of 11 healthy volunteers found that 200 mg itraconazole with 240 mL of double strength grapefruit juice, results in an approximately 45% reduction in AUC of itraconazole and its active metabolite.[19, 20]
Loratadine	Increased serum concentrations possible, may increase the risk of adverse effects	**Unlikely to be clinically significant**	Theoretical	Unknown/Rapid	Theoretical interaction based upon the knowledge that it is metabolised by CYP3A4. However, loratadine can also be metabolised by CYP2D6 and it is therefore postulated that the existence of two elimination pathways renders loratadine less susceptible to drug interactions. No clinical studies found.[13,18]
Methadone	Increased serum concentrations may increase the risk of adverse effects	**Clinical significance unknown**	Theoretical	Unknown/Rapid	Theoretical interaction based upon the knowledge that methadone is metabolised by intestinal CYP3A4. Unlikely to be clinically significant as only one report of any CYP3A4 inhibitor interacting with methadone could be found (fluconazole increasing methadone concentrations by approximately 25%).[18]
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	A study of 10 healthy volunteers found that 200 mL double strength grapefruit juice taken three times a day slightly delayed the absorption of an oral dose of 16 mg of methylprednisolone. Tmax‡, Cmax, AUC and the half-life were prolonged. However, there were no significant differences in plasma cortisol concentrations.[21]
Midazolam	Increased bioavailability and pharmacodynamic effects of midazolam	**Little clinical significance**	Fair	Moderate/Rapid	Eight healthy volunteers were given 200 mL of grapefruit juice before either oral (15 mg) or intravenous (5 mg) midazolam. The kinetics of intravenous midazolam were unaffected. With oral midazolam AUC increased by 52%, Tmax by 79%. However, distribution and elimination were not affected.[10,13]
Nicardipine Nifedipine	Increased serum concentrations increasing the risk of adverse effects, however no adverse haemodynamic effects reported	**Insignificant**	Good	Moderate/Rapid	With grapefruit juice (double strength) the bioavailability of oral nifedipine increased by about 33%. This may be of concern in patients with severe hypertension or stable angina. Another study comparing regular strength grapefruit juice demonstrated no significant differences in plasma concentrations or clinical symptoms.[13]

Drug	*Possible adverse event*	*Clinical importance*	*Extent of evidence*	*Severity/ Onset*	*Summary of study data*
Nimodipine	Increased nimodipine bioavailability. No adverse haemodynamic effects reported.	**Unlikely to be clinically significant**	Poor	Moderate/Rapid	The results of one study of eight healthy young males showed that co-administration of nimodipine and grapefruit juice increased the bioavailability of nimodipine by 51%.[13,22]
Omeprazole	None	**Insignificant**	Poor	Moderate/Rapid	The co-administration of omeprazole and grapefruit juice decreases the formation of omeprazole sulfone (mediated by CYP3A4) but does not inhibit the formation of 5-hydroxyomeprazole, which is mediated by CYP2C19.[23]
Pimozide	Possible increased serum concentrations	**Theoretical. Unlikely to be clinically significant.**	Poor	Major/Rapid	Grapefruit juice may inhibit the metabolism of pimozide resulting in increased concentrations of pimozide. No clinical trials reported.[13]
Pravastatin	None	**Insignificant**	Poor	None/Not specified	During a crossover study of 11 healthy volunteers, grapefruit juice had no significant effect on the AUC, Cmax, Tmax or elimination half-life of pravastatin. This may be due to the fact that CYP3A4 enzymes play a minor role in the metabolism of pravastatin.[3]
Prednisolone	None	**Insignificant**	Poor	None/Not specified	Bioavailability of prednisolone is unaltered by grapefruit juice.[12]
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	During a crossover study of 12 healthy volunteers, grapefruit juice decreased the AUC of the major metabolite, but not of quinidine itself, and Tmax for quinidine was increased. Neither toxicity nor prolonged haemodynamic changes were observed.[24]
Quinine	None reported	**Insignificant (its metabolism is predominantly hepatic rather than intestinal therefore grapefruit juice has a minimal effect)**	Poor	None/Not specified	During a crossover study of 10 healthy volunteers, grapefruit juice had no effect on the AUC, Cmax, Tmax or elimination half-life. Quinidine is metabolised by CYP3A4 in the liver, however the lack of effect of grapefruit juice on quinine kinetics supports the theory that grapefruit juice inhibits CYP3A4 mainly in the gut wall, and drugs with high oral bioavailability will be less affected by grapefruit juice than those with low bioavailability.[13]
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	During a crossover study of eight healthy volunteers, the pharmacokinetics of intravenous saquinavir were not altered significantly. However, the AUC of oral saquinavir increased by 50%, but the Cmax, Tmax and terminal half-life were not significantly altered. The oral bioavailability, calculated as the dose-corrected ratio of the AUCs after oral and intravenous saquinavir, increased 100% after pretreatment with grapefruit juice.[25]

Drug	*Possible adverse event*	*Clinical importance*	*Extent of evidence*	*Severity/ Onset*	*Summary of study data*
Sertraline	Grapefruit juice may inhibit the metabolism of sertraline elevating serum concentrations	**Clinical significance unknown. No increase in adverse effects reported. Monitor patients for altered response.**	Poor	Moderate/Delayed	Five depressed patients stabilised on sertraline for more than six weeks were administered 240 mL of grapefruit juice over seven days. The mean trough concentration increased from 13.6 to 20.2 microgram/L. No difference in the frequency of adverse effects was reported. Grapefruit juice had minimal effects on sertraline metabolism in one patient, possibly due to the high inter-individual variability in CYP3A4 activity. A larger study is needed to show the clinical significance of the interaction.[26]
Simvastatin	Increased serum simvastatin concentrations resulting in increased adverse effects (e.g. myopathy, rhabdomyolysis)	**May be clinically significant**	Fair	Moderate/Rapid	A randomised, two-phase crossover study of 10 healthy volunteers found a ninefold increase in Cmax and a 16-fold increase in AUC when grapefruit juice (200 mL) was compared with water.[27]
Sirolimus	Increased plasma concentrations resulting in an increased risk of toxicity	**May be clinically significant**	Fair	Moderate/Delayed	Avoid grapefruit juice – use orange juice instead.[13]
Tacrolimus	Significantly increased plasma concentrations and increased risk of toxicity	**May be clinically significant**	Poor	Moderate/Delayed	Avoid grapefruit juice – use orange juice instead.[13]
Theophylline	None	**Insignificant**	Poor	None/Not specified	Grapefruit juice has been shown to inhibit the metabolism of caffeine, which is metabolised by CYP1A2, therefore a study of its effect on theophylline was commenced. During a crossover study of 12 healthy volunteers, grapefruit juice had no effect on the AUC, Cmax, Tmax or elimination half-life.[13]
Triazolam	Increased serum triazolam concentrations resulting in increased sedation	**Unlikely to be clinically significant**	Fair	Minor/Rapid	A randomised, two-phase crossover study of 10 healthy volunteers found a significant increase in Cmax and AUC. This caused a slight decrease in psychomotor performance.[4,13]
Verapamil	None	**Insignificant**	Poor	None/Not specified	Ten hypertensive patients on long-term verapamil therapy participated in a two-day crossover study investigating the effect of 200 mL of grapefruit juice. Bioavailability (Cmax, Tmax and AUC) of verapamil was unaltered by grapefruit juice.[28]
Warfarin	None	**Insignificant**	Poor	None/Not specified	A randomised, two-phase crossover study of 10 healthy volunteers found no change in INR.[29]

* AUC total area under the plasma drug concentration-time curve
† Cmax maximum plasma drug concentration during a dosing interval
‡ Tmax time required to achieve a maximal concentration

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Mechanism of interaction

One mechanism of interaction is thought to be through the inhibition of CYP3A4-mediated metabolism (often first-pass metabolism) by a component of grapefruit juice, which increases concentrations of the affected drug. CYP3A4 is located in both the liver and the enterocytes (small intestine epithelial cells). One study concluded that a mechanism for the effect of grapefruit juice (studied on the felodipine/grapefruit juice interaction) was a selective downregulation of CYP3A4 in the small intestine. There may in fact be a post-transcriptional decrease in the amount of small intestinal CYP3A enzyme rather than a competitive or non-competitive inhibition of the enzymes. Individual disparity in the magnitude of the interaction with grapefruit juice appears at least partially explained by innate differences in baseline small bowel CYP3A4 protein content.[4,15,17,30]

Flavonoids and furanocoumarins present in grapefruit juice are thought to be the substances that can inhibit CYP3A4, although the exact components, which inhibit CYP3A4 enzymes, have not been clearly identified. One study has indicated that grapefruit juice contains six major constituents; naringin (NAR) the most prevalent flavonoid, naringenin (NGN) present as a conjugate in grapefruit juice, quercetin (QTN), 6',7'-dihydroxybergamottin (DHB), bergamottin (BEG) and kaempferol. The study investigated the effects of these constituents on saquinavir metabolism. It was determined that DHB and BEG inhibit CYP3A4-mediated metabolism *in vitro* and may also be responsible for the mechanism-based dose regulation of intestinal CYP3A4 caused by grapefruit consumption. DHB and NAR inhibited the P-glycoprotein (Pgp)-mediated drug efflux and this may contribute to the observed effects of grapefruit juice *in vivo*. However, a final decision on which flavonoid is the major active ingredient has not been reached.[4,10,15,30,31]

A second mechanism of interaction is possibly through Pgp. This is located in the apical brush border of the enterocytes. Pgp is a member of the adenosine triphosphate-binding cassette (ABC) superfamily of proteins. The role of the Pgp transporter is to carry lipophilic molecules from the enterocyte back into the intestinal lumen. After uptake by the enterocyte, many lipophilic drugs are either metabolised by CYP3A4 or pumped back into the lumen by the Pgp transporter. Pgp and CYP3A4 may act in tandem as a barrier to oral delivery of many drugs. Inhibition of either or both systems can increase the bioavailability of a drug.[15] *In vivo* data show that grapefruit juice may activate Pgp in intestinal cell monolayers. Therefore if grapefruit juice has this activating effect on Pgp *in vivo*, reducing drug bioavailability might counteract the increased bioavailability seen with inhibition of CYP3A. However, clinical studies with grapefruit and cyclosporin have revealed conflicting evidence, suggesting that there may be *in vivo* inhibition of Pgp. Further evidence is therefore required before the effect of grapefruit juice on Pgp is fully understood.[15]

What is the duration of the inhibition?

Inhibition of CYP3A4 by grapefruit juice can last a number of hours. Increased felodipine concentrations have been observed even when the drug was taken 24 hours after drinking a glass of juice.[1] In one study the extent of the increase in felodipine AUC and Cmax was maximal when grapefruit juice was given four hours before, or simultaneously with, the drug. The half-life of the effect of grapefruit juice on CYP3A4 was estimated in one study to be 12 hours.[30]

Does the quantity of juice matter?

Several studies appear to show that one glass of regular strength juice has a similar effect on the concentrations of felodipine as 2–3 glasses of double strength juice. However, consumption of very large quantities of grapefruit juice (6–8 glasses per day) may lead to inhibition of hepatic CYP3A4, whereas lower quantities (up to three glasses per day) seem to have intestinal activity only.[15]

All the studies, which investigate the effects of grapefruit on the metabolism of drugs, use grapefruit juice (either single or double strength) to study its effects. The effects are best seen when 240 mL of double strength reconstituted grapefruit juice is taken simultaneously with the drug, or if 240 mL of regular strength grapefruit juice is drunk three times a day.[4]

Is the effect of ingesting a whole grapefruit the same as ingesting the juice?

At the present time there are no studies which indicate that eating either a half or a whole grapefruit will have any effect on a drug's metabolism. However, one study has reported that blended grapefruit segments and an extract from grapefruit peel caused a similar interaction as the juice, with felodipine.[15]

Do other citrus fruits have the same effect?

Sweet orange juice does not inhibit CYP3A4. Seville (or bitter) orange juice does inhibit CYP3A4 but, unlike grapefruit juice, does not influence cyclosporin disposition.[32] It is not known whether other drugs which interact with grapefruit juice may also interact with this type of orange juice. Tangelos (a hybrid between grapefruit and tangerine) have not been tested for drug interactions.

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