

Drug Interactions with Grapefruit and Related Citrus Fruits Excerpted from Food-Medication Interactions 14th Edition



Many drugs interact with grapefruit (juice, segments, extract and certain related citrus fruits, e.g. Seville oranges, pummelos, and some exotic orange varieties). Several components in grapefruit called furanocoumarins (two of the most common are bergamottin and 6'7'-dihydroxybergamottin) irreversibly inhibit cytochrome P450 3A4 isoenzymes (3A4) in the intestinal wall, decreasing the pre-systemic metabolism of affected drugs taken up to 72 hours after grapefruit consumption. Intestinal 3A4 activity can remain inhibited during this time, as the body produces more enzymes. Greater amounts of 3A4-metabolized drugs can then enter the systemic circulation. The resulting increase in drug levels can lead to an increase in therapeutic effect, adverse effects and/or toxicity. Interactions are most pronounced for drugs that normally undergo a large amount of pre-systemic metabolism (low oral bioavailability). Limited evidence indicates that following intake of very large amounts of grapefruit, hepatic 3A4 may also be inhibited.

If a drug's metabolic pathways are known, it may be possible to predict if an interaction with grapefruit could occur. Grapefruit weakly inhibits intestinal cell wall p-glycoprotein (p-GP), an efflux pump in enterocytes that actively secretes some absorbed drugs back into the gut lumen. Not all 3A4-metabolized drugs are p-GP substrates. Organic anion transporting polypeptide (OATP) is another transporter system affected by grapefruit. Drugs handled by OATP may have *decreased* absorption when taken with grapefruit, possibly leading to loss of efficacy. Emerging information indicates bergamottin inactivates cytochrome p450 2B6 and 3A5 isoenzymes, potentially causing drug interactions with substrates of these isoenzymes.

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| 1 -Manufacturer recommends avoidance. | 7 - Not metabolized by 3A4, no interaction suspected. |
| 2 - Use with grapefruit/related citrus only on advice of a physician. | 8 - No interaction when drug administered parenterally. |
| 3 - Serum/Plasma level monitoring required/recommended. | 9 - Withdrawn from market. |
| 4 - Minor interaction, not clinically significant. | 10 - Blood levels/bioavailability decreased. |
| 5 - Interaction suspected, but no formal studies. | 11 - Risk higher in CYP 2D6 poor metabolizers. |
| 6 - No formal studies, but lacks a cardiotoxic metabolite. | |

Medications that should be avoided with grapefruit

amiodarone (Cordarone)8	cisapride (Propulsid, Prepulsid)9	pimozide (Orap)5
astemizole (Hismanal)5, 9	colchicine5	quinidine (Quinaglute, Quinidex)8, 10
atorvastatin (Lipitor)	eletriptan (Relpax)5	sildenafil (Viagra)
budesonide (Entocort)8	etoposide (Vepesid)8, 10	simvastatin (Zocor)8
bupirone (BuSpar)	halofantrine (Halfan)	sirolimus (Rapamune)1, 5
cerivastatin (Baycol)5, 9	lovastatin (Mevacor)	terfenadine (Seldane)9
cilostazol (Pletal)5	mifepristone (Mifeprex)5	ziprasidone (Geodon)5

Use with grapefruit with caution

albendazole (Albenza)	erythromycin (Eryc, E-mycin, Erythromid, Erybid)8	nisoldipine (Sular)
alfentanil (Alfenta)8	eszopiclone (Lunesta)5	oxybutynin (Ditropan)5
alfuzosin (Uroxatral)5	felodipine (Renedil, Plendil)	propafenone (Rythmol)5, 11
almotriptan (Axert) 5	fexofenadine (Allegra)10	quetiapine fumarate (Seroquel)5
aprepitant (Eemend)5	fluvoxamine (Luvox)	quinine
aripiprazole (Abilify) 5	gefitinib (Iressa)5	ramelteon (Rozerem)5
bupropion (Wellbutrin, Zyban)5	imatinib mesylate (Gleevec/Glivec)5	saquinavir (Invirase)2
carbamazepine (Tegretol)3	indinavir (Crixivan)10	sertraline (Zoloft)
cinacalcet (Sensipar)5	itraconazole (Sporanox)10	solifenacin (Vesicare)5
clomipramine (Anafranil)	losartan (Cozaar)	tacrolimus (Prograf)2, 3, 8
cyclosporine (Neoral)2, 3, 8	methadone (Dolophine)5	tamoxifen (Nolvadex)5
darifenacin (Enablex)5	methylprednisolone (Medrol)8	tamsulosin (Flomax)5
delavirdine (Rescriptor)5	midazolam (Versed)8	tolterodine (Detrol)5
dextromethorphan	montelukast (Singulair)5	triazolam (Halcion)
diazepam (Valium)8	nicardipine (Cardene)8	trazodone (Desyrel)5
dofetilide (Tikosyn)5	nifedipine (Procardia)	
efavirenz (Sustiva)5	nimodipine (Nimotop)	
erlotinib (Tarceva)5		

Medications with no significant interaction with grapefruit

Drugs in this section have all been studied with grapefruit, and found to have either a minimal/negligible interaction.

acebutolol (Monitan, Sectral)4	ethinyl estradiol4, 8	scopolamine (Hyoscine)4, 8
alprazolam (Xanax)4	fentanyl (Actiq)4, 8	17- β estradiol4, 8
amlodipine (Norvasc)4	haloperidol (Haldol)8	telithromycin (Ketek)4
amprenavir (Agenerase)4, 10	lansoprazole (Prevacid)4, 8	theophylline (Theo-Dur, Uniphyl)
caffeine4, 8	levothyroxine (Eltroxin, Synthroid)4, 8	verapamil (Calan, Isoptin, Verelan)8
carvedilol (Coreg)4	omeprazole (Losec, Prilosec)4	warfarin (Coumadin)8
clarithromycin (Biaxin)	phenytoin (Dilantin)8	
clozapine (Clozaril)4	pravastatin (Pravachol)	
digoxin (Lanoxin)8	prednisone (Deltasone)	
diltiazem (Cardizem)4, 8		
eplerenone (Inspra)4		

Medications considered safe for use with grapefruit

cetirizine (Zyrtec, Reactine)6	fluvastatin (Lescol)7	praziquantel (Biltricide)
desloratadine (Aerius, Clarinex)7	loratadine (Claritin)6	rosuvastatin (Crestor)7

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