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## *Graedons' Guide to*

# *Grapefruit Interactions*

## **Drugs & Grapefruit**

- Some prescription drugs interact with grapefruit, but most do not.
- People who love grapefruit may not have to give it up. There may be alternate medicines that do not interact.
- Dosage adjustments are another way to continue to enjoy grapefruit even if a medicine does interact. This requires very careful monitoring and communication between patient and physician.
- People vary in their susceptibility to this interaction. Some are very sensitive, while others are virtually immune.
- Medications given by injection or transdermally are not affected by grapefruit interactions, which happen primarily in the digestive tract.

Grapefruits have long been considered "funny" fruit. In Canada there's a parlor game called "Pamplemousse," the French name for grapefruit. But as much as we love the taste of grapefruit, there is nothing funny about the way it interacts with many drugs.

The story of this interaction goes back to the early 1990s in London, Canada. A team of researchers at The University of Western Ontario were interested in a possible interaction between alcohol and a heart and blood pressure medicine called felodipine (**Plendil**). There was reason to suspect that alcohol might modify the metabolism of this medicine.

One of the researchers, Dr. David Bailey, was charged with the task of finding some way to disguise the flavor of the alcohol. A non-drinker and athlete (the first Canadian to run a four-minute mile), Dr. Bailey found the taste of pure alcohol in orange juice so disagreeable that he set out to find something better for his subjects. He and his wife spent a Friday evening tasting various concoctions and finally settled on double-strength grapefruit juice.

To the researchers' surprise, there was no important interaction between alcohol and felodipine. But blood levels of the medicine were three times higher than expected. According to one of the team members, J. David Spence, M.D. (Professor of Neurology, Internal Medicine and Pharmacology, Director of the Stroke Prevention and Atherosclerosis Research Centre, University of Western Ontario), "We faxed over to the drug company in Sweden

and said, 'Come on, you guys must have sent us the 20 mg tablets instead of the 5 mg.'" The company responded with an offer to analyze the tablets, which were indeed 5 mg strength. "So David Bailey took felodipine with water one day and measured his blood levels and then took felodipine with grapefruit juice the next day. The blood levels were about four times higher. We didn't have to wait for blood levels to come back from Sweden because he turned red and felt lightheaded and faint." The team's subsequent study was published in *Lancet* in 1991 (Vol 337, pp 268-269).

At first these data were ignored by the medical community. Experts in drug metabolism were fascinated, however, and followed up with further studies to confirm the interactions of grapefruit and grapefruit juice with felodipine and other medicines. Scientists know that something in grapefruit inhibits an important enzyme, CYP 3A4, in the wall of the intestine. This enzyme is critical for the breakdown of hundreds of medications. When its effectiveness is compromised, blood levels of such drugs can rise and trigger undesirable side effects. The responsible compound in grapefruit remains elusive. Experts believe it may be a bioflavonoid, perhaps a bergamottin derivative, which may contribute to grapefruit's distinctive flavor.

Researchers have found the grapefruit interaction so compelling that they have extended their

Research on grapefruit interactions is far from complete. Most drugs have not been studied for their potential to interact with foods in general or grapefruit in particular. Some, like digoxin (**Lanoxin**) and warfarin (**Coumadin**) have been shown not to interact significantly, but many other interactions may yet be discovered.

investigations to dozens of medicines. At last count more than 30 drugs are affected, including some of the most popular products in the pharmacy. It is likely that many more will be discovered over the next few years, but we provide details on some of the more well-established and important interactions in the following pages.

The “grapefruit effect” is highly variable. It depends in large measure on the amount of the enzyme CYP 3A4 that is found in the digestive tract. Some people naturally have a lot of this enzyme. Others, relatively little. Just as eye color

and fingerprints differ from one person to the next, so too our enzymes can be variable. Those with a lot of this enzyme are the most susceptible to the grapefruit effect. They also appear vulnerable to red wine, which has a somewhat similar impact as grapefruit.

There is no easy way to tell if you have a lot or a little CYP 3A4. For some reason, older people may be more susceptible to the effect. This interaction needs to be taken quite seriously, as it may result in dosages that are much higher than the physician intended and lead to dangerous reactions.

## FREQUENTLY ASKED GRAPEFRUIT QUESTIONS

### **Does fresh grapefruit have the same effect as grapefruit juice?**

Yes. The substance in grapefruit that produces this interaction is found in the fresh fruit as well as in the juice.

### **How long does the grapefruit effect last? Can I have my grapefruit in the morning and take my pills safely later in the day?**

No. The grapefruit interaction is long lasting. Initially it was thought to last “only” eight hours. More recently, investigators have found that the effect is measurable for at least 24 hours and may linger up to two days.

### **Do oranges or other citrus fruits interact in a similar way?**

No. The active ingredient in grapefruit has not been definitively identified, but it is thought to be a bioflavonoid (possibly a derivative of bergamottin). Most other citrus fruits do not contain this compound. There is one other type of fruit that does interact like grapefruit. Seville oranges, used primarily for making marmalade, are quite bitter. They too can affect the same enzyme as grapefruit and would interact in a similar manner.

### **Do I have to give up grapefruit completely if it interacts with my medicine?**

Not necessarily. There are several factors to consider. Some people are resistant to the grapefruit effect because they have lower levels of CYP 3A4. Unfortunately, this is not something most clinical laboratories are likely to measure. An occasional half grapefruit or glass of juice may not raise blood levels enough to cause serious problems, but before doing this experiment, check with your doctor.

### **Can I use the grapefruit effect to reduce my dose of medicine?**

Possibly. But only with careful medical supervision. This is actually a fascinating area of research. Think of grapefruit as a turbo-booster for a car. It gives extra power. Instead of working to the person's detriment, this potential could be harnessed to lower the dose of an expensive medicine. Cyclosporine (**Sandimmune**, **Neoral**) is given to people to modify the immune system and keep them from rejecting a transplanted organ. With frequent blood tests and careful monitoring by the transplant team, grapefruit juice may be used to gradually reduce the amount of cyclosporine needed.

Calcium channel blockers are widely prescribed for high blood pressure and heart problems. The original discovery that grapefruit juice could interact with drugs was made during research on a calcium channel blocker called felodipine (**Plendil**). In some people, **Plendil** blood levels may rise as much as 300% to 500% in the presence of grapefruit. This caused flushing, lightheadedness and faintness in a healthy, athletic researcher. An elderly person with a heart problem might have even more trouble.

Other calcium channel blockers

Millions of people take statin-type cholesterol-lowering drugs daily to reduce their risk of heart disease. Some of the most popular medicines in this class are affected by grapefruit. Blood levels of **Mevacor** and **Zocor** are significantly increased by grapefruit. **Lipitor** is also affected, though to a lesser degree. Our concern is that if the dose of any of these medications is substantially higher than normal, there may be an in-

Several medicines used to treat anxiety and help people get to sleep also appear to interact with grapefruit. The one most strongly affected is buspirone (**Buspar**), generally used for daytime anxiety. Side effects that might be expected as a result of unexpectedly high blood levels include dizziness, drowsiness, nausea, headache or fatigue. Diazepam (**Valium**), another anti-anxiety drug that was once

Amiodarone is a valuable heart rhythm regulator, but dose is critical. Grapefruit juice dramatically increases blood levels of this medicine. Side effects of excessive amiodarone include low blood pressure, dizziness, heart problems and liver toxicity.

may also be affected by grapefruit flavonoids. Short-acting nifedipine has been controversial because research shows that people taking high doses of this drug are at increased risk of death. The National Heart, Lung and Blood Institute has urged doctors to use "great caution" in prescribing this medicine, but grapefruit juice could convert a normal dose of **Procardia** to a significantly higher one.

Verapamil is also affected by grapefruit juice. The interaction appears less intense, however, and may not be significant.

Increased risk of side effects such as muscle pain or weakness. Kidney damage is a rare complication. An occasional glass of grapefruit juice may not pose a problem, but someone who regularly consumes grapefruit or juice may be taking a chance. Pravastatin (**Pravachol**) and fluvastatin (**Lescol**) do not appear to be affected by grapefruit. They may offer a reasonable alternative for grapefruit lovers.

very popular, also appears to interact with grapefruit juice, though not as strongly as **Buspar**. Excessive levels of diazepam could cause drowsiness, incoordination and confusion.

The sleeping pills **Halcion** and **Sonata** may also be affected by grapefruit. Sedation may be greater than expected and the effects of the medicine might linger longer.

Quinidine is less strongly affected by grapefruit than amiodarone. Nonetheless, because dosage is always a worry with this drug, we would caution against regular consumption of grapefruit or grapefruit juice for anyone on quinidine.

## **Calcium Channel Blockers**

Felodipine  
(**Plendil**)  
Nicardipine  
(**Cardene**)  
Nifedipine  
(**Adalat**)  
(**Procardia**)  
Nimodipine  
(**Nimotop**)  
Nisoldipine  
(**Sular**)  
Verapamil  
(**Calan**)  
(**Covera-HS**)  
(**Isoptin**)  
(**Verelan**)

## **Cholesterol Lowering Drugs**

Atorvastatin  
(**Lipitor**)  
Lovastatin  
(**Mevacor**)  
Simvastatin  
(**Zocor**)

## **Sleeping Pills & Anti-Anxiety Drugs**

Buspirone  
(**Buspar**)  
Diazepam  
(**Valium**)  
Triazolam  
(**Halcion**)  
Zaleplon  
(**Sonata**)

## **Heart Drugs**

Amiodarone  
(**Cardarone**)  
(**Pacerone**)  
Quinidine  
(**Quinaglute**)  
(**Quinidex**)

Cyclosporine has revolutionized transplant surgery. Without this drug many patients would reject the new heart or kidney they receive. Grapefruit can increase cyclosporine blood levels dramatically. With careful monitoring by a transplant team, this effect could be useful, because it would allow lower doses of an expensive medication. But a patient un-

aware of the interaction could suffer serious side effects, including kidney problems, diarrhea, high blood pressure and seizures. Tacrolimus and sirolimus, two other transplant drugs, also interact with grapefruit. This could contribute to toxicity.

Estrogen in the form of estradiol is affected by grapefruit. This means a woman taking birth control pills or hormone replacement therapy might have higher levels of estrogen circulating in her bloodstream if she also consumes grapefruit.

This could lead to side effects such as nausea or breast tenderness. Lifetime exposure to high levels of estrogen is associated with an increased risk of developing breast cancer.

Several protease inhibitors, medications used to treat AIDS, appear to interact with grapefruit juice. The interaction has been confirmed with saquinavir. Amprenavir, nelfinavir and ritonavir are expected to interact with grapefruit as

well, though this hasn't been confirmed by studies. Accurate dosing for these AIDS drugs is extremely important. Grapefruit could make this more complicated and requires close supervision.

Carbamazepine is officially an anticonvulsant prescribed primarily for epilepsy. But physicians have found it useful for a wide range of other conditions, including pain (trigeminal neuralgia, neuropathy, etc), psychiatric problems (bipolar disorder, schizophrenia, etc), cocaine and alcohol withdrawal problems and restless leg

syndrome. Grapefruit raises blood levels of carbamazepine by about 40 percent and could increase the risk of toxicity. Symptoms could include dizziness, drowsiness, nausea, vomiting, urinary difficulties, rash and unsteady gait.

## ***Transplant Drugs***

Cyclosporine  
(**Neoral**)  
(**Sandimmune**)  
Sirolimus  
(**Rapamune**)  
Tacrolimus  
(**Prograf**)

## ***Estrogen***

Estradiol  
(**Estinyl**)  
(**Estrace**)  
Birth Control Pills  
(Assorted brands)

## ***HIV/AIDS Drugs***

Ritonavir  
(**Norvir**)  
Saquinavir  
(**Fortovase**)  
(**Invirase**)

## ***Epilepsy Drug***

Carbamazepine  
(**Tegretol**)

## **OTHER POSSIBLE GRAPEFRUIT INTERACTIONS**

A number of other medications also appear to interact with grapefruit, or might be expected to interact with grapefruit based on the fact that they are metabolized by the cytochrome P450 3A4 enzyme. The antidepressants nefazodone (**Serzone**) and trazodone (**Desyrel**) are among them.

Antipsychotic medications may also interact. A case report on two children indicates that levels of clomipramine (**Anafranil**), prescribed primarily for obsessive-compulsive disorder, may increase measurably when combined with grapefruit. The schizophrenia medicine quetiapine (**Seroquel**) is expected to interact with grapefruit as well. Side effects that might occur could include drowsiness, headaches, dizziness, involuntary muscle twitching and restlessness.

The cortisone-like drug methylprednisolone (**Medrol**) is mildly affected by grapefruit. Although there is some question about the significance of this interaction, we would urge caution as some people may be more sensitive than others to increased steroid effects. A similar concern exists for the impotence medicine sildenafil (**Viagra**). There is good theoretical reason to suspect that grapefruit would boost blood levels of this drug and one case report demonstrated high blood levels in an older man who took **Viagra** with grapefruit juice. This combination could possibly lead to low blood pressure, fainting and more serious cardiovascular complications.

Other drugs that could potentially interact with grapefruit include the asthma medicine montelukast (**Singulair**), the blood pressure pill losartan (**Cozaar**), the Alzheimer's drug donepezil (**Aricept**), the breast cancer medicine tamoxifen (**Nolvadex**), the prostate medication tamsulosin (**Flomax**) and the nonsedating antihistamines loratadine (**Claritin**) and fexofenadine (**Allegra**). The significance of any of these interactions is unknown.