

UCLA
Nutrition Bytes

Title

Grapefruit Juice and Some Oral Drugs: A Bitter Combination

Permalink

<https://escholarship.org/uc/item/7cn8p8k9>

Journal

Nutrition Bytes, 5(1)

ISSN

1548-4327

Author

Vu, Minh Chau

Publication Date

1999

Peer reviewed

Introduction

When Seldane® was first released in 1985, it immediately became a very popular allergy medicine. Seldane®, or terfenadine, was one of the first antihistamines that relieved allergy symptoms such as watery eyes, sneezing, and runny nose without causing any drowsy side effects. However, in early 1997, the FDA recommended that it be removed from the market due to its potentially dangerous side effects affecting the heart. There were several documented reports of patients dying due to fatal arrhythmias. The most significantly documented case was a patient who, in addition to taking terfenadine twice a day for over a year, also consumed grapefruit juice 2 to 3 times a week. On the day of his death, he had taken 2 glasses of grapefruit juice before collapsing due to fatal cardiac arrhythmia. At the time, it was not known that this drug interacted with grapefruit juice, and his death was attributed to terfenadine toxicity (1).

It was not until a study conducted to test the interaction between felodipine, a calcium channel antagonist, and ethanol that by serendipity, grapefruit juice was discovered to alter drug metabolism (2). In that study, grapefruit juice was used to mask the taste of ethanol. Bailey et al. demonstrated that the combination of ethanol and felodipine resulted in orthostatic hypotension and lower blood pressure. Although the same concentration of felodipine was administered to each treatment arm, plasma felodipine concentration was five-fold greater with ingestion of grapefruit juice (3). As a result, it was proposed that grapefruit juice prevented the metabolism of felodipine by suppressing the oxidative effects of Cytochrome P450 3A4 (CYP3A4) in the intestinal wall.

Mechanism

Felodipine is a calcium channel blocker that is used to dilate blood vessels and decrease hypertension. Felodipine is completely absorbed in the gastrointestinal wall after oral administration. After its absorption, it undergoes high first-pass metabolism. First pass metabolism refers to drugs that are extensively metabolized by the liver and small intestine before reaching systemic circulation. Only drugs administered orally are affected by first pass metabolism because they must be absorbed through the gastrointestinal wall. Therefore, the drug amount that is actually available to the body is significantly less than the amount initially administered. Because Felodipine is usually highly metabolized, its bioavailability is very low, averaging only 15%.

CYP3A4 is an important enzyme involved in the metabolism of over 60 different drugs, including felodipine and other drugs that have been found to interact with grapefruit juice. Studies have shown that grapefruit juice suppresses the activity of CYP3A4 and other CYP3A isozymes located specifically in the small intestine, allowing a greater amount of felodipine to circulate systemically. Lown et al. showed that following consumption of a single dose of grapefruit juice (equivalent to one 250 ml glass), there was a decrease of immunoreactive CYP3A4 and CYP3A5 by 62% in the small intestine, but levels of CYP3A4 and CYP3A5 were unaffected in the liver and colon, respectively (3,4). When the amount of CYP3A4 mRNA was analyzed, it was discovered that the mRNA concentrations were unchanged. This implied that grapefruit juice did not

decrease the synthesis of CYP3A4 but rather accelerated its degradation through mechanism-based enzyme inhibition (3,10).

What are some other drugs that interact with grapefruit juice?

Terfenadine

In addition to affecting felodipine, grapefruit juice increases the bioavailability of many other compounds also metabolized by CYP3A4. Grapefruit juice only affects drugs taken orally, and not those administered intravenously. Terfenadine, as was mentioned before, is a potent antihistamine that is well absorbed after oral intake and undergoes complete first pass metabolism by CYP3A4. Levels of terfenadine are therefore rarely detected in the plasma unless there is overdose, liver disease, or inhibition of CYP3A4 metabolism via concomitant administration of erythromycin, ketoconazole, or itraconazole (3). CYP3A4 converts terfenadine into two different metabolites: terfenadine carboxylate and azacyclonol. Terfenadine carboxylate is the active ingredient that confers antihistamine activity and does not possess the same toxic activity as its parent compound, terfenadine. Terfenadine is a potent blocker of the delayed rectifier potassium channel in cardiac myocytes (5). These channels are responsible for repolarizing myocytes after an action potential. Consequently, terfenadine delays the time needed for contracted myocytes to relax, thereby causing abnormal heart rhythm. A study conducted by Rau et al. showed that people given grapefruit juice in addition to terfenadine had detectable plasma terfenadine concentrations. In addition, levels of terfenadine carboxylate plasma concentrations were also lower with grapefruit juice (5). Increased levels of terfenadine can prolong QT intervals and cause ventricular arrhythmias.

Cyclosporine

Cyclosporine is an immunosuppressive drug widely used in patients who received organ transplantation. Cyclosporine levels must be very carefully monitored because of its narrow therapeutic window and dangerous side effects, such as nephrotoxicity, hypertension, and cerebral toxicity (6). Cyclosporine is metabolized by CYP3A in the small intestine and in the liver. Furthermore, grapefruit juice inhibits its metabolism only for a short duration, so adverse reactions due to decreased metabolism of cyclosporine have not been reported (6).

HIV protease inhibitor- Saquinavir

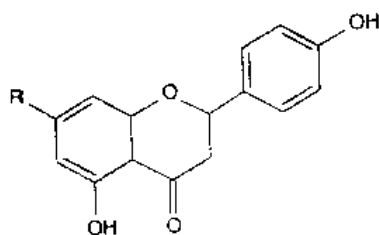
Contrary to the toxic effects seen with felodipine and terfenadine, grapefruit juice has been found to have a therapeutic effect when consumed with saquinavir, an HIV protease inhibitor. Saquinavir has very low bioavailability because of its first pass elimination by CYP3A4. Its low bioavailability is a major problem in serving as an anti-retroviral drug because patients need to consume many pills at once that are very expensive (14). However, a study showed that just one glass of grapefruit juice could increase its bioavailability two-fold in HIV negative volunteers, suggesting that this may be one way of increasing saquinavir bioavailability (14).

What is the active ingredient in grapefruit juice?

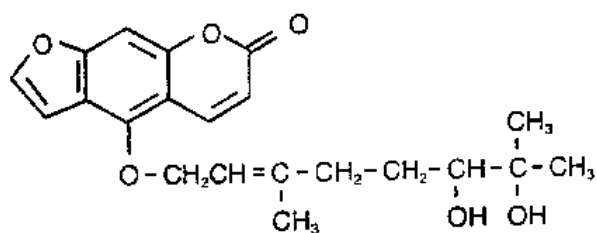
Flavonoids are substances that are numerous in plants and citrus fruits and are able to inhibit oxidative drug metabolism (3). Unlike grapefruit juice, though, orange juice and other citrus drinks have not been found to alter drug metabolism when taken concomitantly with drugs that are metabolized by CYP3A4. This is because naringin, a certain flavonoid, is unique to grapefruit juice; orange juice contains different flavonoids that appear to confer no inhibitory activity (3,7,8). It was first thought that naringin was the compound responsible for the inhibitory effects on CYP3A4. Naringenin, which is a metabolite of naringin, is a strong suppressor of cytochrome P450 enzymes, particularly CYP3A4 (7). However, when pure naringin was administered orally, it could not reproduce the same grapefruit effects, suggesting that some other constituent may be responsible (8,9,10). In addition, flavonoids are not mechanism-based inactivators, and grapefruit juice inhibits CYP3A4 via this pathway.

Recent studies have shown that coumarin and psoralen derivatives may be the culprits responsible for inhibiting first pass metabolism by CYP3A4. These compounds are known to be mechanism-based inhibitors of cytochromes P450 (10). Psoralen and its derivatives are abundant in grapefruit juice and are located primarily in the grapefruit peel (7). Because these compounds are highly lipophilic, they are readily absorbed in the gastrointestinal wall and extensively metabolized. Once absorbed, psoralens seem to inhibit CYP3A4 by binding reversibly to the substrate binding site. In many cases, psoralen metabolites are active compounds that can inactivate the enzyme irreversibly. One such metabolite, 6'7'-dihydroxybergamottin (DHB), is a potent inhibitor of CYP3A4 enzymes in rat liver microsomes (11). In a study conducted by Schmedlin Ren et al. , the authors showed that when DHB was incubated with recombinant CYP3A4, there was rapid degradation of the enzyme. In addition, several DHB metabolites were detected following incubation. As a result, it was proposed that DHB might be a substrate for CYP3A4, behaving also as a potent competitive inhibitor (10). The active ingredients in grapefruit juice are now attributed to psoralens, primarily DHB, with naringenin perhaps contributing a small inhibitory role (Figure 1).

Because DHB is found in only certain parts of the grapefruit, the way grapefruit juice is prepared can affect the degree of drug interaction. DHB is the main component responsible for mediating the grapefruit effect in reconstituted frozen concentrate, the most common form of juice consumption (10). An epoxide of DHB, found only in the grapefruit peel, is also a potent inhibitor of CYP3A4. Frozen concentrates therefore have a higher amount of active ingredient than freshly squeezed juice or the fruit itself, because the pressure exerted to prepare the frozen concentrate squeezes the grapefruit peel containing the DHB epoxide into the juice. Grapefruit and freshly squeezed juice do not contain this epoxide, and thus have a lower amount of active ingredient (10).



Chemical structure of naringin and naringenin. For naringenin, R = OH; for naringin, R = β -neohesperidose.



6', 7' - dihydroxybergamottin

Figure 1. Active ingredients in grapefruit juice. (Adapted from Bailey and Fuhr)

How much grapefruit juice does one need to drink before it starts to exert its effect?

Studies have shown that just one glass (250 ml) of grapefruit juice is enough to prevent drug metabolism. Surprisingly, additional ingestion of grapefruit juice does not potentiate its inhibitory effect (5). In a study where two groups were given either single or double strength grapefruit juice, the concentration of plasma terfenadine was the same between both groups (5). Another study using grapefruit juice and felodipine produced similar results. This suggests that "the inhibition of the pre-systemic metabolism is already fully developed after a single glass of juice"; in other words, one glass of grapefruit juice is enough to cause maximum inhibition of CYP3A4 (12). Furthermore, long term ingestion of grapefruit juice does not potentiate its inhibitory effects. Lundahl et al. showed that when people consumed grapefruit juice and felodipine together for 14 days straight, there was no difference in metabolic inhibition between day 1 and day 14 (12).

How long do the effects of grapefruit juice last?

It only takes a few initial hours to cause rapid suppression of CYP3A4. Levels of CYP3A4 were found to be drastically decreased within 2-4 hours after ingesting a single glass of grapefruit juice (10). However, the effects of grapefruit juice can last over 24 hours since last consumption (13).

Why does the grapefruit effect last so long? One hypothesis suggests that the active ingredient of grapefruit juice has a long half-life and is slowly absorbed from the gastrointestinal tract (13). Grapefruit juice may also cause irreversible inactivation of the enzyme. In this case, the body would have to synthesize new CYP3A4 before any drug metabolism or elimination is to occur (13).

Clinical Implications

Because grapefruit juice inhibits CYP3A4, it has the potential of interacting with many drugs whose interactions have not yet been studied. If a patient has adapted to a higher bioavailability of circulating drugs due to consumption of grapefruit juice, taking the patient off grapefruit juice might cause an adverse effect because now the drug strength has significantly decreased. Therefore, consistency of grapefruit intake while taking medication is very important. It is sometimes recommended that if a person has always

taken grapefruit juice with their drug, then they should continue to do so. However, if a person has never taken grapefruit juice while on medication, then they should avoid the juice.

One problem with grapefruit juice is that the concentration of the active ingredients is extremely variable; even the way it is prepared can affect how much active component is present. As a result, the consequences of grapefruit-drug interaction are highly unpredictable. Although consistency between drug and grapefruit intake is important, people who are on medication are advised to refrain from drinking grapefruit juice because of the unknown variability.

In addition, because grapefruit juice potentiates the effect of many expensive medications, such as cyclosporine and HIV protease inhibitors, it has been suggested that patients drink grapefruit juice along with their medication to reduce the amount of drugs that they need to take. Although this idea does sound promising, not enough research has been conducted to assess its safety.

Additionally, no testing to date has verified the ingredients in the over the counter supplements, because the FDA does not regulate the supplements. For this reason, little is known about any impurities that may cause serious side effects if administered in large doses. Finally, pyruvate is not stable as a compound and may degrade over time.

Until extensive experimentation has been conducted on male and female athletes in various modes of strength and endurance exercises it is impossible to draw conclusions about the possible beneficial effects of pyruvate and dihydroxyacetone on athletic performance. Although experimental results do look promising, it is important to realize that controlled laboratory conditions are very different from real world application.

To make conclusions about DHAP supplementation with regard to athletic importance, several double-blind peer-reviewed clinical trials must be conducted on male and female athletes in a wide range of endurance and strength exercises, using doses of the supplement that will be used in real world application. Only after these studies have been conducted and the results verified and replicated will it be possible to accept the claims made by multilevel marketing distributors, health food stores, and body building magazines.

REFERENCES

1. Spence, JD. Drug interactions with grapefruit: whose responsibility is it to warn the public? *Clinical Pharmacology and Therapeutics*. 1997; 61 (4): 395-400.
2. Bailey, DG, Spence JD, Edgar B, Bayliff CD, Arnold JMO. Ethanol enhances the hemodynamic effects of felodipine. *Clinical Investigation of Medicine* . 1989; 12: 357-362.
3. Gailey, DG, Arnold JMO, Spence JD. Grapefruit juice- drug interactions. *British Journal of Clinical Pharmacology* . 1998; 46: 101-110.

4. Lown KS, Bailey DG, Fontana RJ, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *Journal of Clinical Investigation*. 1997; 99 (10): 2545-33.
5. Rau SE et al. Grapefruit juice-terfenadine single-dose interaction: magnitude, mechanism, and relevance. *Clinical Pharmacology and Therapeutics* . 1997; 61(4): 401-9.
6. Adrianus AMG et al . The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clinical Pharmacology and Therapeutics*. 1995; 57(3): 318-24.
7. Fuhr, U. Drug Interactions with Grapefruit Juice- Extent, probable mechanism and clinical relevance. *Drug Safety* . 1998; 18(4): 251-72.
8. Ameer, B, Weintraub, RA. Drug Interactions with grapefruit juice. *Clinical Pharmacokinetics* . 1997; 33(2): 103-21.
9. Bailey DG, Arnold JMO, Munoz C, Spence JD. Grapefruit juice-felodipine interaction: mechanism, predictability and effect of naringin. *Clinical Pharmacology Therapeutics* . 1993; 53: 637-42.
10. Schmiedlin-Ren,P et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit constituents. Decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. *Drug Metabolism and Disposition* . 1997; 25(11): 1228-33.
11. Edwards DJ, Bellevue FH, Woster, PM. Identification of 6'7'-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice. *Drug Metabolism Disposition* . 1996; 24: 1287-90.
12. Lundahl, JUE et al. The interaction effect of grapefruit juice is maximal after the first glass. *European Journal of Clinical Pharmacology*. 1998; 54: 75-81.
13. Lundahl, JUE et al. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Journal of Clinical Pharmacology* . 1995; 49: 61-67.
14. Kupferschmidt, H et al. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. *British Journal of Clinical Pharmacology*. 1998; 45 (4): 355-9.

Additional Readings

1. Rang, HP, *Pharmacology* . Churchill Livingstone, 1991.

2. Advise for the Patient- Drug Information in Lay Language . USPDI-Vol. II, 19th edition. 1999.