# The Grapefruit Juice Effect

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## Abstract

A drug interaction is the effect that a substance can have when taken together with a drug. Grapefruit juice has proven to be a source of interaction with many drugs, causing increased bioavailability, leading to possible toxicity and increased instances of side effects. This paper discusses the mechanisms of the interaction and the components of grapefruit juice responsible for the interaction, as well as two classes of drugs that are affected, calcium channel antagonists and HMG-CoA reductase inhibitors, and possible ways to avoid the interaction. The mechanisms are inhibition of the enzyme cytochrome P-450 3A4 (CYP3A4) and the transport molecule P-glycoprotein. Furancoumarins are responsible for the interaction. In general, drugs that are affected have a low oral bioavailability and are substrates of CYP3A4. The interaction is best avoided by not drinking grapefruit juice, or choosing a drug that doesn't interact. Other possibilities include juice low in furanocoumarins due to harvest factors, and furanocoumarin free juice. In conclusion, one should exercise caution unless it has been proven that the drugs being taken do not interact with grapefruit juice.

## Introduction

In 1997, twenty one percent of the households in America chose to buy grapefruit juice to drink as their breakfast beverage. In recent years, the public have realized the importance of including antioxidants in their diets, and the choice of grapefruit juice, which contains those compounds, reflects that awareness. Several chronic diseases, most importantly cardiovascular disease and some cancers, could possibly be prevented by flavenoids and other components of grapefruit juice. Additionally, there was a study that was done that showed that grapefruit and grapefruit juice might promote weight loss (Mertens-Talcott, et. al. 2006). Due to its possible health benefits, it's hard for many people to believe that grapefruit juice can have an adverse effect when taken together with many common medications.

A drug interaction is a name given to the effect that any substance can have when ingested together with a medication. The possible effects fall into two categories: pharmacokinetics and pharmacodynamics. Pharmacokinetics includes changes in absorption, distribution, metabolism, and excretion. Pharmacodynamics is the description of the relationship between the concentration of the drug and its effect (Mertens-Talcott, et. al. 2006). Grapefruit juice causes pharmacokinetic interactions. When taken together with grapefruit juice, many medications display an increased bioavailability (Fuhr, 1998). This leads to undesired effects, such as decreased efficiacy or toxicity. Increased side effects can occur as well (Mertens-Talcott, et. al. 2006). The unpleasantness of toxicity can cause patients to stop taking the drugs, and in extreme cases, toxicity can even cause death (Bailey, Dresser, 2004).

The phenomenon of the grapefruit juice- drug interaction was discovered by chance in 1989. An experiment was being done to determine if there was an interaction between felodipine, a calcium channel antagonist, and ethanol. Grapefruit juice was used to mask the taste of the ethanol. When the results were analyzed, it was discovered that the concentrations of felodipine were significantly higher than those recorded in other experiments, and the subjects had lower blood pressure and higher instances of unwanted side effects. Further testing was performed to try to discover the cause, and it was found that the increased concentration was a result of the grapefruit juice. Since then, numerous drugs have been tested, and many have been found to interact with grapefruit juice (Dahan, Altman, 2004). This research paper will discuss the possible mechanisms behind this phenomenon and the components of grapefruit juice thought to cause the interaction. The effect and clinical relevance of grapefruit juice on two classes of cardiovascular medications, calcium channel antagonists and HMG-CoA reductase inhibitors, will be analyzed, and several ways of avoiding the interac-

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tions will be explored as well.

## Methods

Research was done using Touro College's search engines such as ProQuest, and MEDLINE, and most frequently, EBSCO. The method of research included evaluating original studies and peer reviewed articles. Keywords such as "grapefruit juice", "drug interaction", and specific names of drugs were used.

## Mechanisms of Action

There are several possible mechanisms that have been suggested to explain the interaction. Since the interaction only takes place with drugs that are ingested orally, the mechanism must occur at some point during the digestion process (Mertens-Talcott, et. al. 2006).

## Cytochrome P-450 3A4

Cytochrome P450 is a family of enzymes that is responsible for the breakdown and detoxification of, among other substances, steroids, environmental carcinogens, and drugs (Girennavar, et. al. 2007). Cytochrome P-450 3A4 (CYP3A4) specifically is the isoenzyme highly prevalent in the human digestive system, found in the small intestine and the liver. Drugs that are metabolized by CYP3A4 have low oral bioavailability, so only a small amount of the total that is ingested enters circulation. Because of this, larger doses are administered so that enough of the drug will be available to cause the desired effect. If CYP3A4 is inhibited, greater oral bioavailability results, and there is a possibility for undesired effects to occur (Bailey, Dresser, 2004).

Grapefruit juice has been shown to inhibit CYP3A4 in in vitro studies. In one study, the enzyme was tested with 1%, 10%, and 25% concentrations of different species of grapefruit and pummel juices. Significant inhibition was observed, especially at concentrations of 10% and 25%. At those concentrations, inhibition ranged from 96.69% to 99.88% (Girennavar, et. al. 2007). In another study that used human liver microsomes, inhibition was observed as well. (Seden, et. al. 2010)

Grapefruit juice has been proven to be an inhibitor of CYP3A4 in in vivo studies as well. Diminished CYP3A4 enzyme presence, but not mRNA, has been observed after drinking just one 300 mL glass of grapefruit juice. The decreased levels indicate that the inhibition is not competitive in nature. (Bailey, Dresser, 2004). Additionally, an investigation that measured CYP3A4 levels after six days of drinking grapefruit juice recorded greatly decreased amounts of the enzyme but not of the CYP3A4 mRNA (Seden, et. al. 2010). Due to these observations, it can be assumed that grapefruit juice most likely does not inhibit production of the enzyme. Instead, the juice causes destruction of the enzyme through suicide or mechanism-based inhibition. A component of grapefruit juice is thought to be converted to a reactive metabolite that bonds to CYP3A4 and causes inactivation (Bailey, Dresser, 2004).

If this were the case, synthesis of new enzymes would be required for restoration of CYP3A4 activity, which explains the prolonged effect that grapefruit juice can have. Studies performed with felodipine to determine the length of time of the effect grapefruit juice support the theory. It was shown that the maximum effect can still be observed when the juice is ingested 4 hours before the drug is administered, and increased levels of felodipine were still recorded when there was a 24 hour interval between juice and drug intake (Bailey, Dresser, 2004). Recovery times of 72 hours for nisoldipine (Bailey, Dresser, 2004) and 74 hours for midazolam (Mertens-Talcott, et. al. 2006) have been observed as well.

It is interesting to note that the effect of the interaction varies widely among individuals. Those with initial high CYP3A4 activity have been shown to have greater inhibition than those with naturally lower activity of the enzyme. Therefore, ingestion of grapefruit juice together with an affected drug by these individuals will cause a greater increase in drug concentration than would result in subjects with low CYP3A4 activity (Mertens-Talcott, et. al. 2006).

## P-glycoprotein

P-glycoprotein is an ATP-dependent drug transporter. It is an efflux pump located in the small intestine, liver, kidneys, and at the blood brain barrier. P-glycoprotein decreases the bioavailability of many drugs by limiting the amount absorbed from the intestines (Bailey,

Dresser, 2004). P-glycoprotein has many substrates, and a majority of them overlap with the substrates of CYP3A4. (Seden, et. al. 2010)

The inhibition of P-glycoprotein by grapefruit juice was first demonstrated by the increased uptake of vinblastine into Caco-2 cells. Since vinblastine is a substrate of both CYP3A4 and P-glycoprotein, no definite conclusion could be drawn regarding the inhibition of P-glycoprotein (Mertens-Talcott, et. al. 2006). A study done using human renal proximal cells proved that grapefruit juice does in fact inhibit P-glycoprotein expression and activity (Romiti, et. al. 2004) Another study investigated P-glycoprotein inhibition in Caco-2 cells as well, using colchicine as the probe. Grapefruit juice caused increased transport of colchicine into the cells. As is the case with vinblastine, colchicine is both a CYP3A4 and a P-glycoprotein substrate, so the cause of the increased uptake can't be credited solely to P-glycoprotein inhibition. The same study investigated colchicine permeability in the small intestine of rats in situ. It was found that grapefruit juice significantly increased the permeability of the drug (Dahan, Amidon, 2008). In an additional investigation, rats were given talinolol, a substrate of P-glycoprotein that does undergo metabolization. Because of that, there is no potential for the inhibition of CYP3A4 to interfere with the results. When given together with grapefruit juice, concentrations of talinolol were increased (Bailey, Dresser, 2004).

Although the in vitro studies demonstrate that there is a possible inhibition of P-glycoprotein by grapefruit juice, there have been difficulties in reproducing the effects in human trials (Seden, et. al. 2010). Digoxin is another drug that is known to be an unmetabolized substrate of P-glycoprotein. The drug did not display a great change in bioavailability when administered with grapefruit juice as compared to water. But since digoxin has a high bioavailability of 70-80%, it is not expected that inhibition of P-glycoprotein would drastically change its concentration (Bailey, Dresser, 2004).

Although research has yet to produce clear proof, the above studies demonstrate that there is an interaction between grapefruit juice and P-glycoprotein. Further studies must be done to determine the extent of the inhibition and how significantly it affects grapefruit juice-drug interactions. According to the current information, it seems to be that the interaction is mainly caused by inhibition of CYP3A4, and that inhibition of P-glycoprotein plays a small role as well.

## Components of Grapefruit juice Possibly Responsible

There are hundreds of chemical components present in grapefruit juice. The amounts present in a specific juice depend on a variety of factors, including the genetic background of the plant, and the conditions during the growth, maturity, harvesting and processing of the fruit. Most of the constituents are present in other citrus fruits as well, but the amounts of the specific ones differ among the species. Since juices from numerous sources have displayed interactions with drugs, it seems that the component or components that cause the interaction are always present. Two of the typically present substances, flavonoids and furanocoumarins have been presented as the most probable sources of the grapefruit juice effect (Fuhr, 1998).

## Flavonoids

The flavonoid naringin is present in much higher levels in grapefruit juice than in other citrus fruit juices. Naringenin, the active metabolite of naringin, is known to be a strong inhibitor of CYP3A4. Several in vitro studies have shown that both naringin and naringenin are able to inhibit the metabolic process of the drugs tested (Fuhr, 1998). Additionally, it has been demonstrated that naringenin has the ability to inhibit P-glycoprotein in human renal proximal cells (Romiti, et. al. 2004).

Although these trials seem promising, human trials have not gotten conclusive results. Studies that gave subjects naringin in the form of capsules or in solution did not observe any significant increase in concentrations of the drugs that were tested. Furthermore, in a study in which naringin was removed from grapefruit juice, CYP3A4 activity was still inhibited (Fuhr, 1998).

## Furanocoumarins

Furanocoumarins are mainly found in the peels of grapefruit, but there are significant amounts present in the juice as well (Fuhr, 1998). The most abundant, bergamottin and its metabolite 6'7'-dihydroxybergamottin (DHB), have

been identified as CYP3A4 inhibitors. Several in vitro studies have proven this.

The individual furanocoumarins have been isolated and tested in several studies. In one study, DHB, bergamottin, paradisin A, bergaptol and geranylcuomarin were tested for the extent of the inhibition that they caused. It was found that paradisin A was the strongest, followed by DHB, then bergamottin, then bergaptol, and finally geranlycoumarin (Girennavar, et. al. 2007). Although DHB is not the strongest, it is the most abundant which is most probably why the inhibitory effect is generally attributed to its presence. In another study, the furanocoumarins were isolated and tested as a whole to determine their overall inhibitory capacity. When all were combined, the inhibition was similar to that observed with whole grapefruit juice. Removing any one of the furanocoumarins from the mixture decreased the inhibition, which presents the possibility that all of furanocoumarins play a role in the grapefruit juice effect (Dahan, Altman, 2004).

Further reinforcement of the role of furanocoumarins can be seen in studies that evaluated the effect of furanocoumarin-free grapefruit juice. In one study, most of the furanocoumarins were removed using Aspergillus niger, a strain of fungus. The altered juice was tested in vitro and found to have a reduced inhibitory effect (Myung, et. al. 2008). In another study, approximately 99% of the furanocoumarins were removed using food grade solvents and absorption resins. In vitro, the processed juice did cause some inhibition, but to a markedly lesser extent than did whole grapefruit juice. The same study performed a human trial, using felodipine as the probe. It was found that when compared to orange juice, the control, furanocoumarin-free grapefruit juice had no great effect on the pharmacokinetics of the drug. This was the first study to show that the grapefruit juice effect can be credited completely to furanocoumarins (Paine, et. al. 2006).

### Drugs that Exhibit an Interaction

The drugs that are affected by grapefruit juice follow a general trend. First of all, because the interaction occurs in the gastrointestinal tract, the medication must be ingested orally. Second, the drug in question must be either metabolized by CYP3A4 or transported by P-glycoprotein. Finally, since grapefruit juice increases bioavailability, the drug must have a normally low bioavailability (Bailey, Dresser, 2004).

### Dihydropyridine Calcium Channel Antagonists

Calcium channel antagonists are vasodilators that are used to treat hypertension and other cardiovascular disorders. Excessive vasodilation can result in headaches, swelling of the ankles, and facial flushing. These are not serious side effects, but they are unpleasant enough to cause patients to stop taking the medication, thus leaving their conditions untreated. The more serious side effects include severely low blood and pressure myocardial infarction (Bailey, Dresser, 2004).

Felodipine, the drug with which the grapefruit juice interaction was first observed, has been studied extensively. It has an absolute bioavailability of 15% (Bailey, Dresser, 2004). Over the course of these studies it has been determined that depending on the amount and timing of the ingestion of grapefruit juice, the concentrations of felodipine can increase to between double and triple the usual levels. Greater instances of adverse side effects were observed as well (Fuhr, 1998).

Nifedipine, another calcium channel antagonist with low oral bioavailability, has been shown to be affected by grapefruit juice as well. In a single case study on a 50 year old man, 500 ml of grapefruit juice caused nifedipine levels to more than double (Nakagawa, Gotu, 2010). Although this was a single case study, and therefore no definite conclusions can be drawn, the results match those of larger studies. In another study, sixteen subjects drank 250 ml of grapefruit juice. The observed result was much less dramatic than that of other studies, but there was an increase in bioavailability. This can possibly be explained by the smaller amount of grapefruit juice administered. In most other studies, the amount ingested was between 400 and 500 ml (Odou, et. al. 2005). Other drugs in this class that have displayed an interaction are nicardipine, nisodipine, and nitrendipine. The average changes in concentration for the above range from 1.5 to four times the normal amount (Bailey, Dresser, 2004).

The final calcium channel antagonist, amlodipine, has a high oral bioavailability of between 64% and 80%

(Seden, et. al. 2010). Because of this, it is not expected to interact with grapefruit juice, and studies support this hypothesis. In the same single case study discussed previously, grapefruit juice did not affect the plasma concentration of the drug (Nakagawa, Gotu 2010). In a study performed using twenty volunteers, 240 ml of grapefruit juice was ingested together with the amlodipine, and an additional 200 ml was taken each day for 8 days following drug administration. Bioavailability was not altered significantly (Vincent, et. al. 2000).

## HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, commonly known as statins, are used to lower cholesterol. They have the potential to cause serious toxicity. Side effects range from diffuse myalgia, or muscle pain, to rhabdomyolysis, which is severe skeletal muscle degeneration. Acute renal failure is a possibility as well (Bailey, Dresser, 2004).

Simvastatin, lovastatin, and atorvastatin are all metabolized by CYP3A4 and therefore have low bioavailability. Simvastatin and lovastatin are inactive forms that are converted to their active acid forms by esterases. Before the conversion, they are extensively metabolized by CYP3A4, resulting in a bioavailability of approximately 5% (Bailey, Dresser, 2004). In one study, ten volunteers ingested 200 ml of grapefruit juice for two days before and then together with a dose of simvastatin. The average increase in concentration was 3.6 times greater than that observed with water (Lilja, et. al. 2004). In other studies that tested simvastatin and lovastatin, the average increase was 15-fold the normal (Bailey, Dresser, 2004).

Atorvastatin has a bioavailability of 12%. In a study using eight subjects, grapefruit juice was ingested for three days before and concomitantly with atorvastatin. Juice was also administered 4 and 12 hours after drug intake. Concentrations increased between 1.5 and 1.7-fold (Ando, et. al. 2005). In another study that surveyed twenty subjects, grapefruit juice was consumed at regular intervals before, during and after administration of atorvastatin. The average increase that was observed was 83% (Fukazawa, et. al. 2003). Finally, a much larger study was performed using 130 subjects. Patients drank grapefruit daily for ninety days together with their medication, and there was a small but still statistically significant increase in concentrations (Reddy, et. al. 2011).

Pitavastatin, a synthetic statin, has a bioavailability of 60% (Ando, et. al. 2005). It is metabolized not by CYP3A4, but by CYP2C9, and to some extent by CYP2C8 (Seden, et. al. 2010). In the study that surveyed the effects of grapefruit juice on atorvastatin in eight subjects, pitavastatin was tested as well. It was found that the juice only slightly increased concentrations of pitavastatin in the blood (Ando, et. al. 2005).

Like pitavastain, pravastatin is not metabolized by CYP3A4. Pravastatin was surveyed in the second study described for atorvastatin that tested twenty subjects. No significant effects were recorded (Fukazawa, et. al. 2003). Two other statins, fluvastatin and rosuvastatin, have not yet been tested (Seden, et. al. 2010). But fluvastatin is a CYP2C9 substrate, and rosuvastatin appears not to be a substrate of either CYP3A4 or P-glycoprotein, so no interactions are predicted (Bailey, Dresser, 2004).

## How to Avoid the Interaction

The simplest way to avoid the interaction would be to abstain from drinking grapefruit juice while undergoing treatment with a drug that is known to, or has been predicted to, interact with grapefruit juice. If the patient has no interest in giving up the juice, the next best solution would be to select one of the drugs that have been proven to have no interaction with the juice. However, if that specific drug is required, and changing to a non-interacting medication is impossible, there are several methods that might limit the possibility of an interaction occurring.

As it has been proven that furanocoumarins are the cause of the grapefruit juice-drug interaction, the ideal way to minimize the possibility of an interaction occurring is to limit exposure to furanocoumarins. Below are several possible ways in which the levels of furanocoumarins can be reduced.

## Harvest Factors and Different Species of Grapefruit

It has been proven that the maturity, location, processing, and storage of grapefruits and grapefruit juice affects the levels of furanocoumarins present in the final ingested product. Furanocoumarins are molecules that are

produced in times of stress so there are many factors that affect their levels. It was found that furanocoumarin levels are highest at the beginning of season, and that they decrease throughout the season. In evaluating location, it was discovered that in general, grapefruits grown in Florida and California had higher levels than grapefruits grown in Texas. Hand squeezing versus commercial processing tests revealed that levels were higher in hand squeezed juice. Post-harvest, furanocoumarin levels were lowered when stored at both 24 and 9°C. Finally, levels were evaluated in processed juice stored in three different types of containers: cans, cardboard bottles, and cartons. All displayed a decrease in levels over time, but the cartons contained the highest levels of furanocoumarins (Girennavar, et. al. 2008). Based on these findings, those who would like to drink grapefruit juice and minimize the possibility for an interaction should choose commercially processed juice stored in cans or bottles, and made from organic grapefruits grown in Texas that were harvested late in the season.

## Furanocoumarin-Free Grapefruit Juice

Furanocoumarins have been extracted from grapefruit juice for studies, but commercial furanocoumarin-free juice has not been developed. Based on the studies, there are two possible ways to extract them. In one study, the fungi Aspergillus niger was incubated with grapefruit juice. The fungus was able to absorb most of the non-polar furanocoumarins, but not the polar ones, and not the flavonoids. The juice was then tested on CYP3A4, and it was found that inhibition of the enzyme was significantly reduced. This method still needs further development though, because the strain of fungus that was used could produce toxins. For the removal of furanocoumarins from grapefruit juice by fungus to become possible commercially, a method employing food-grade, edible fungi must be developed (Myung, et. al. 2008). In another study, furanocoumarin-free grapefruit juice was created using food-grade solvents and absorption resins. 99% of the furanocoumarins were able to be removed. When tested in a human trial, the juice had no effect on the concentrations of felodipine (Paine, et. al. 2006).

## Conclusion

As seen in the above studies, grapefruit juice has the potential to interact with many drugs. Any medication that is either a substrate of CYP3A4 or transported by P-glycoprotein can possibly be affected when taken together with grapefruit juice. The components in the juice that are responsible for the interaction are the furanocoumarins, which bind to and inactivate CYP3A4 and P-glycoprotein. Avoidance of the interaction is best accomplished by not drinking grapefruit juice, or selecting a drug that is known not to interact. If such actions are not possible, juice that was processed so as to minimize furanocoumarins might be a possibility, and there is a chance that furanocoumarin-free grapefruit juice will be developed sometime in the future.

Since there are so many drugs that have the possibility of interaction, it is important to simply be aware of this phenomenon. Patients must know to let their doctors know if they drink grapefruit juice habitually and to ask if any medications that they are on can interact. Unless it has been proved that there is no possibility of a reaction, any drug that might interact based on the method in which it's metabolized should be treated as if it is privy to the grapefruit juice-drug interaction.

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