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DRUG INTERACTIONS WITH GRAPEFRUIT JUICE

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ABSTRACT

Concomitant intake with grapefruit juice increases the concentrations of many drugs in humans. The effect seems to be mediated mainly by suppression of the cytochrome P450 enzyme CYP3A4 in the small intestine wall. This results in a diminished first pass metabolism with higher bioavailability and increased maximal plasma concentrations of substrates of this enzyme. The effect was most pronounced in drugs with high first pass degradation. The components of grapefruit juice which are the most probable causes of the interaction are furanocoumarins derivatives, but the flavonoid naringenin may also contribute. Concomitant grapefruit juice intake does not generally decrease the variability of drug pharmacokinetic parameters. Therefore, it is recommended that patients abstain from drinking grapefruit juice when they are taking a drug that is extensively metabolised, unless a lack of interaction has already been demonstrated for that drug. It is also recommended that drugs possibly interacting with grapefruit juice should be appropriately labelled.

1. INTRODUCTION

The grapefruit (*Citrus paradisi*) grows in clusters (like grapes) on a tree. Grapefruit were initially discovered growing in the West Indies in the 1800s, and then brought to the United States and Asian countries. Grapefruit is believed to have evolved from the pummelo, a citrus fruit from the Rutaceae family (orange family), through mutation or as a hybrid with the common orange. The grapefruit is larger than an orange but smaller than most pummelos and can yield approximately 2/3 cup of juice. There are two major types of grapefruit: white and pink/ ruby red.

The discovery that grapefruit juice can increase the oral availability of some medications was an accidental discovery made when grapefruit juice was used to mask the taste of ethanol in a study involving the calcium channel blocker felodipine. Since then, more different drugs have shown to enhance oral availability when consumed with grapefruit juice. Most of the drugs affected by grapefruit juice have poor and highly variable oral bioavailability. In addition, most of these drugs are chiefly metabolized in the body by CYP3A4, an enzyme present in the liver and intestine.

The major effect of grapefruit juice appears to reduce "first-pass" metabolism by reducing CYP3A4 activity. Because grapefruit juice does not generally affect the systemic clearance of affected drugs, it appears that grapefruit juice selectively reduces intestinal CYP3A4 activity while having little effect on liver CYP3A4. Grapefruit juice has no effect on drug disposition after intravenous administration and does not alter liver CYP3A4 activity.[1]

2. HISTORY[15]

- In 1989 a pharmacological study evaluated the possibility of an interaction between ethanol ingestion and medication with the dihydropyridinecalcium channel blocker - felodipine. Grapefruit juice was used as a flavouring additive during the test. The results of study showed several-fold increase of felodipine concentrations compared to results obtained in other investigations of the drug. Additionally, there were lower blood pressure readings and more adverse effects compared to the group of subjects on felodipine alone. Further investigations revealed that grapefruit juice strikingly elevated felodipine bioavailability and could influence its other pharmacokinetic and pharmacodynamic properties.[15]

3. OBJECTIVES

After completing this continuing education article, the pharmacist should be able to.

1. Identify the mechanism of grapefruit juice-drug interactions and drugs involved with significant grapefruit-drug interactions.
2. Describe potential effects of grapefruit juice-drug interactions.
3. Discuss medications that may be affected and degree of risk associated with common interacting medications.
4. Identify effective alternative medications that do not interact (for patients who do not want to comply with dietary restrictions).
5. Articulate the public health implications of media myths and inaccurate information surrounding this issue.

6. Describe the pharmacist's role in communication the food-drug interaction issue to patients and physicians.
7. Effectively explain drug interaction risk factors and effective, alternative medications for patients.

4. Role of pharmacist in patient communication

Pharmacists play an important role in potential grapefruit-drug interaction situations. Patients need accurate, specific information about the grapefruit juice-drug interaction. When educating a patient regarding a potential grapefruit-drug interaction ask about grapefruit or grapefruit juice consumption. In situations where a patient is taking a medication that interacts with grapefruit juice and does not wish to stop consuming it, the pharmacist might suggest other medication options.

Pharmacists can often predict if a new drug might be a candidate for a significant interaction with grapefruit or its juice by looking at these characteristics.

- Is it metabolized by intestinal CYP3A4?
- Is it given orally?
- Does it have a low bioavailability?
- Does it have a narrow therapeutic index?

The following key messages should be communicated to patients

- Most medications do not interact with grapefruit juice, but if you consume grapefruit or grapefruit juice let your physician or pharmacist know, especially when beginning a new prescription.
- Alternative medications that do not interact with grapefruit may be available if you do not want to stop drinking grapefruit juice or eating grapefruit.

5. Literature reviews

- Bailey DG, Malcolm J, Arnold O, Spence JD. Br J ClinPharmacol, 1998 Aug; 46(2): 101-10.

Grape fruit juice-drug interactions

Bailey DG, et al. 1998 Aug; Grapefruit juice can markedly augment oral drug bioavailability was originally based on an unexpected observation from an interaction study between the dihydropyridine calcium channel antagonist, felodipine, and ethanol in which grapefruit juice

was used to mask the taste of the ethanol. Subsequent investigations showed that grapefruit juice acted by reducing presystemicfelodipine metabolism through selective post-translational down regulation of cytochrome P450 3A4 (CYP3A4) expression in the intestinal wall. Since the duration of effect of grapefruit juice can last 24h, repeated juice consumption can result in a cumulative increase in felodipine AUC and C(max). Clinically relevant interactions seem likely for most dihydropyridines, terfenadine, saquinavir, cyclosporin, midazolam, triazolam and verapamil and may also occur with lovastatin, cisapride and astemizole (Guo et al., 2000).

- Bailey DG, Dresser GK. Am J Cardiovasc Drugs, 2004; 4(5): 281-97.

Interactions between grapefruit juice and cardiovascular drugs

Numerous medications used in the prevention or treatment of coronary artery disease and its complications have been observed or are predicted to interact with grapefruit juice. Such interactions might also cause excessive vasodilatation when hypertension is managed with the dihydropyridinesfelodipine, nicardipine, nifedipine, nisoldipine, or nitrendipine. An alternative agent could be amlodipine. In angina pectoris, administration of grapefruit juice could result in atrioventricular conduction disorders with verapamil or attenuated antiplatelet activity with clopidrogel. Grapefruit juice may enhance drug toxicity for antiarrhythmic agents such as amiodarone, quinidine, disopyramide, or propafenone, and for the congestive heart failure drug, carvediol.

- Bressler R, Geriatrics, 2006 Nov; 61(11): 12-8.

Grapefruit juice and drug interactions. Exploring mechanisms of this interaction and potential toxicity for certain drugs

Concomitant administration of grapefruit juice can increase the plasma concentration of numerous drugs in humans and decrease the concentration of a few others. Such elevations of drug plasma concentrations have, on occasion, resulted in adverse clinical effects. Increased concentrations are primarily mediated by chemicals in grapefruit juice, which inhibit the CYP 3A4 drug-metabolizing enzyme in the small intestines. This inhibition decreases the first-pass metabolism of drugs using the CYP 3A4 intestinal system and increases the bioavailability and maximal plasma drug concentrations (Cmax) of the CYP 3A4 substrates. The effect of grapefruit juice on drug metabolism is most pronounced in drugs with a high first-pass metabolism (eg, felodipine, amiodarone),

- Kiani J, Imam SZ.Nutr J, 2007 Oct 30; 6: 33. Review.

Medicinal importance of grapefruit juice and its interaction with various drugs

Grapefruit juice is consumed widely in today's health conscious world as a protector against cardiovascular diseases and cancers. It has however, been found to be an inhibitor of the intestinal cytochrome P - 450 3A4 system, By inhibiting these enzyme systems, grapefruit juice alters the pharmacokinetics of a variety of medications, leading to elevation of their serum concentrations. Most notable are its effects on the calcium channel antagonist and the statin group of drug.

- Ameer B, Weintraub RA,ClinPharmacokinet, 1997 Aug; 33(2): 103-21. Review.

Drug interactions with grapefruit juice

Some drugs demonstrate a significantly greater (up to 3-fold) mean oral bioavailability on coadministration with grapefruit juice. The components of citrus juice that are responsible for clinical drug interactions have yet to be fully determined. Based on the flavonoid naringin's unique distribution in the plant kingdom, abundance in grapefruit and ability to inhibit metabolic enzymes, naringin is likely to be one of the grapefruit components influencing drug metabolism. Other components present in citrus fruit, such as furanocoumarins,

- Feldman EB, Nutr Rev, 1997 Nov; 55(11 Pt 1): 398-400. Review.

How grapefruit juice potentiates drug bioavailability

Grapefruit juice enhances the effect of some commonly used medications by increasing their bioavailability via the selective down-regulation of a specific subfamily of the cytochrome P450 enzyme system in the small intestine.

- Uno T, Yasui-Furukori N, Curr Clin Pharmacol, 2006 May; 1(2): 157-61. Review.

Effect of grapefruit juice in relation to human pharmacokinetic study

Grapefruit juice (GFJ) interacts with a number of drugs, and can alter pharmacokinetics parameters of the drugs. The predominant mechanisms of GFJ-drug interaction are thought to be due primarily to the inhibition of intestinal CYP3A4 activity without an apparent inhibition of hepatic CYP3A4. GFJ is also an inhibitor of P-glycoprotein, an efflux pump in intestinal cell wall enterocytes, although clinical support for this mechanism remains unclear. In addition, GFJ has recently been shown to be a potent in vitro inhibitor of the organic anion-transporting polypeptides (OATP) 1A2, intestinal uptake transporters of structurally anionic drugs.

- **Drug interaction**

The term interaction is define as alteration in the duration or the magnitude of the pharmacological effect of one drug by another drug when more than one drug is adiministered simulteniosly. thecombin effect may be antagonized or synergistic. In anteagonized or synergistic.in antagonism the effect or one drug is abolished by the other. where as in synergism the effect may be or supra additive. apart from these phenomenon numerous drug interaction are harmful & toxic reaction may occure the incidence of such reactionhas increased mainly due to 3 factors.

1. Drug explosion
2. Availability of potent drug
3. Irrational polypharmacy.[13]

6.Clinical significance of grapefruit drug interaction

After a standard oral dose of a "susceptible" drug, subjects with very low CYP3A4 activity in the intestine will tend to have a relatively high AUC. Grapefruit juice should have a relatively small effect on pharmacokinetics in these individuals because there is little intestinal CYP3A4 activity to inhibit. In contrast, subjects with high intestinal CYP3A4 activity will have a marked increase in AUC when affected drugs are taken with grapefruit juice. A situation in which toxicity could occur would be in patients who have been given higher than usual doses of a susceptible drug and then begin drinking grapefruit juice for the first time. This could occur if the physician increases the drug dose to a desired pharmacologic effect. An additional situation might be when a patient has severe liver disease such that the intestine is the major site for metabolism of the drug. Such a patient would be expected to have high systemic exposure to the drug at usual doses; loss of intestinal CYP3A4 activity would further increase the exposure.

In the future it should be possible to use grapefruit-derived furanocoumarins as additives to certain drugs to improve the oral delivery of some drugs by reducing variability. Such formulations would obviously be no longer susceptible to grapefruit juice interactions. It should also be possible to remove furanocoumarins from grapefruit juice to reduce drug interaction potential.

Finally to thoroughly assess the clinical significance of grapefruit-drug interactions, the type and amount of grapefruit juice must also be considered. This variation between individuals

may be significant and is difficult to predict. The grapefruit-drug interaction appears to affect patients with high quantities of small bowel CYP3A4 isoenzymes.[1]

7.Active components of grapefruit juice

Originally, naringin was thought to be the main component responsible for grapefruit-drug interactions. However, studies have shown naringin to be a weak inhibitor of CYP3A4.[2, 3, 4]

The assumption is that the active components in grapefruit juice do not reach the liver in sufficient concentrations to affect CYP3A4 activity; although a variety of juice components have been implicated to inhibit these enzymes.[4,5]

Furanocoumarins found in grapefruit juice as CYP3A4 inhibitors. The furanocoumarins such as bergamottin was mainly thought to be responsible for the inhibition of intestinal CYP enzymes.[6,7] Bergamottin is present in grapefruit juice in concentrations ranging from 2 to 30 μmol/L. Relative exposure to bergamottin is not known, and doses administered were typically larger than those encountered by humans after normal consumption of grapefruit juice. Thus the relevance of bergamottin in the clinical interaction of grapefruit juice in humans is currently uncertain.[8] But, the most abundant and probably the most important single furanocoumarin is 6,7- dihydroxybergamottin (DHB).[1,9,10]

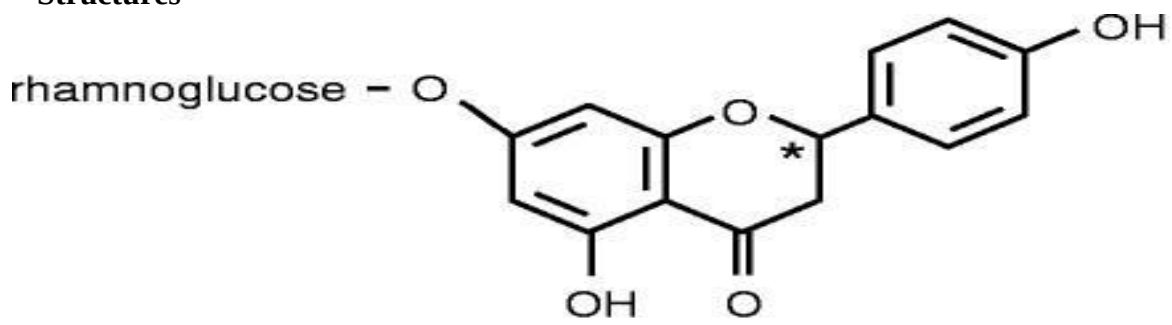
When bergamottin administered as a pure substance enhanced the oral bioavailability of some drugs. However, the effect was substantially less than that produced by grapefruit juice even at markedly higher doses of bergamottin than normally present in the juice. It appears probable that the interaction also involves other furanocoumarins present in whole grapefruit juice, possibly acting in combination by additive or synergistic mechanisms. Bergamottin has systemic availability and is metabolized to 6', 7'- dihydroxybergamottin in humans.[10] recent reports by different groups indicate that 6',7'-dihydroxybergamottin is a more potent mechanism-based inactivator or inhibitor of CYP3A4.

Orange juice has no CYP3A4-inhibiting effects. When orange juice was spiked with a synthetic DHB, however, no significant difference between the degrees of inhibition produced by either of the 2 citrus fruits was observed. Therefore, the DHB component in grapefruit appears to be another potent inhibitor of CYP3A4 and is most likely primarily responsible for the interaction.

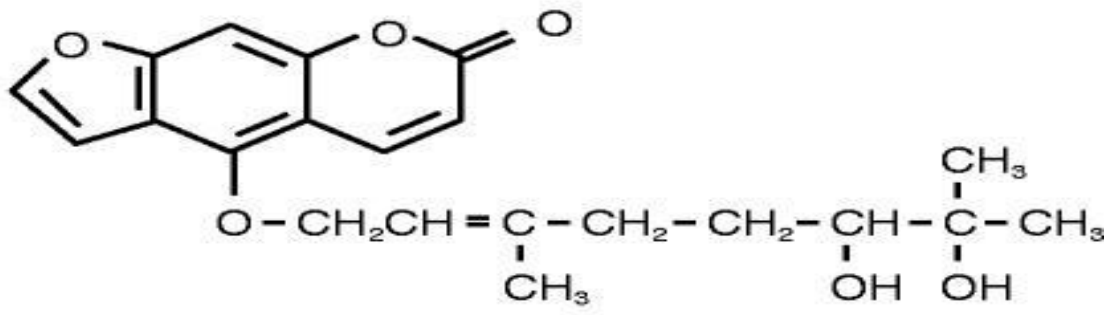
The furanocoumarins are divided into 6 components: 6',7'-dihydroxybergamottin (DHB), GF-I-1, bergamottin (GF-I-2), GF-I-4, GF-I-5 (bergamottin-6',7'-epoxide), and GFI- 6.12 Significant inhibition of CYP3A4 isoenzyme activity is exhibited by DHB, GF-I-1, and GF-I-4 with minimal activity exhibited by bergamottin (a presumed precursor of GF-I-1 and GF-I-4 and a known ingredient of grapefruit essential oil).[11]

The CYP3A4 isoenzyme, which is found in the intestine and liver, accounts for about 40% to 60% of all CYP450 isoenzymes (although it is important to note that grapefruit inhibits CYP450 in the gastrointestinal tract, not the liver) and is involved in the majority of significant CYP450-mediated drug interactions. Inhibition of the CYP3A4 isoenzyme, either reversible or irreversible, will result in a reduced metabolism and metabolic clearance of CYP3A4 substrates.

- **Structures**



Naringin

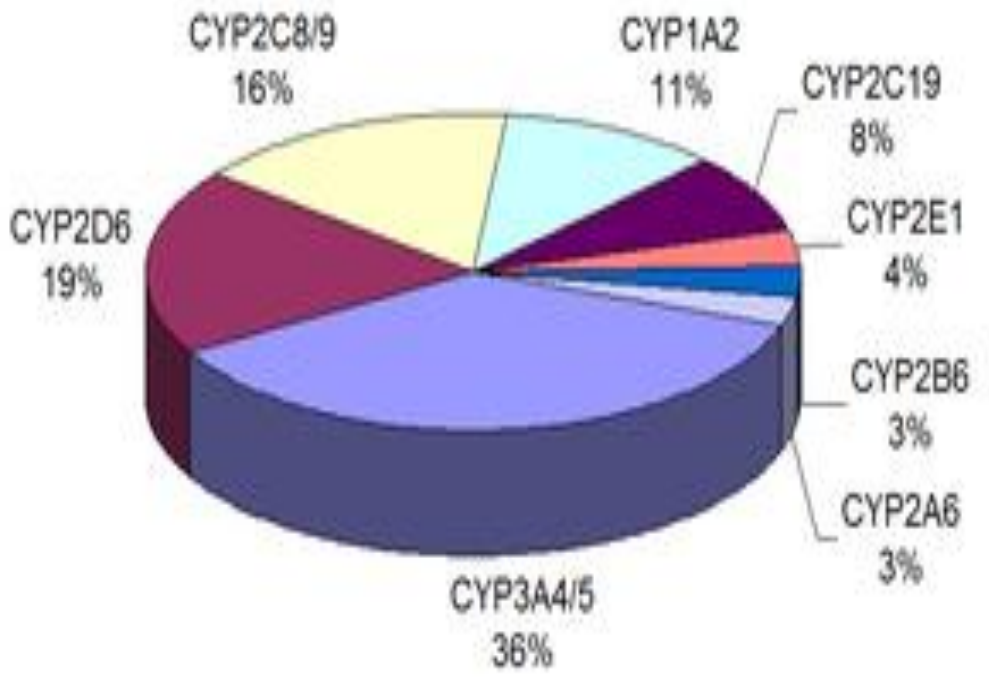


6', 7' – dihydroxybergamottin

8. Drug metabolism by CYPs

CYPs are the major enzymes involved in drug metabolism, accounting for ~75% of the total metabolism.[12] Most drugs undergo deactivation by CYPs, either directly or by facilitated

excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.



Proportion of drugs metabolized by different families of CYPs.

9.Mechanism of action of grapefruit juice components

DHB and other furanocoumarins appear to reduce CYP3A4 activity by three related but distinct mechanisms, as follows.

(1) Competitive or reversible inhibition,

(2) Mechanism-based inactivation (also called irreversible inhibition), and

(3) Actual loss of CYP3A4 enzyme.[1, 9, 17, 18]

The first and most common mechanism is known as competitive inhibition and results from the competition between the inhibitor and substrate for the same CYP isoenzyme required for substrate metabolism and elimination. The effects of competitive inhibition can be observed after administration of the first dose of the inhibitor.

The second mechanism is known as mechanism-based inhibition and occurs with grapefruit juice. The most potent grapefruit components causing a mechanism-based inactivation of CYP3A4 are furanocoumarins, which bind irreversibly to CYP3A4 and permanently inactivate the isoenzyme. The duration of mechanism based inhibition may be longer than competitive inhibition because new CYP3A4 isoenzymes must be synthesized for activity to

be restored. Complete recovery of the CYP3A4 may take 48 to 72 hours after the last exposure to grapefruit juice, which explains why the effects can last for at least 72 hours after drinking grapefruit juice. Most important, because of mechanism-based inhibition, separating the administration of grapefruit juice and substrate drug by a few hours does not minimize grapefruit drug interactions. Pharmacists should advise patients to entirely avoid grapefruit if they are taking medications known to significantly interact with grapefruit juice.

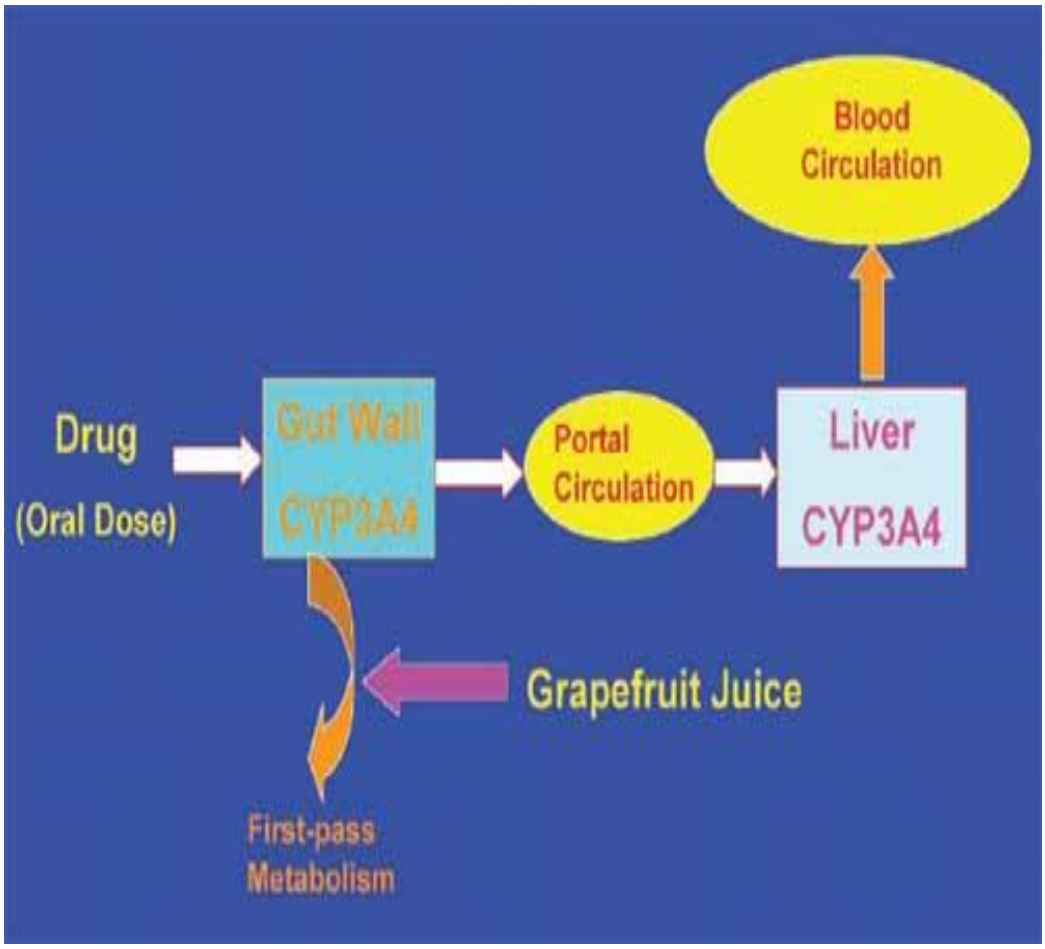
Literature indicated that grapefruit juice at normal volume did not change the terminal half-life (t½) or intravenous pharmacokinetics of drugs. Therefore this pharmacokinetic interaction is thought to be primarily due to grapefruit juice– mediated inhibition of intestinal CYP3A4 activity without apparent inhibition of hepatic CYP3A4 activity. Grapefruit juice inhibition of CYP3A4 in vivo appears to involve irreversible inactivation of CYP3A4, as evidenced by down-regulation of intestinal CYP3A4 protein content without alteration of intestinal messenger ribonucleic acid levels.

The latter mechanism was first noticed when small intestinal biopsy specimens were obtained in healthy volunteers before and after drinking grapefruit juice. With the use of antibodies specific for CYP3A4, it was noted that the intestinal content of CYP3A4 fell by more than 50% after consumption of even a single glass of grapefruit juice. It was then noted that this phenomenon could be reproduced with grapefruit extract or purified DHB in a human intestinal cell line (Caco2) modified to express CYP3A4. Studies performed in these cells have indicated that loss of CYP3A4 in response to DHB exposure is exclusively caused by accelerated degradation of CYP3A4. This is consistent with the observation in humans that grapefruit juice–mediated loss of CYP3A4 protein is not associated with a reduction in CYP3A4 messenger ribonucleic acid.

In addition to the effect on CYP3A4, grapefruit juice may also inhibit the drug transporters P-glycoprotein (P-gp) and organic anion transporting peptide (OATP).[3] P-gp is an efflux membrane transporter pump belonging to the adenosine triphosphate-binding cassette family of proteins. As with CYP3A4, P-gp is found in high concentrations within intestinal enterocytes, the primary site of oral drug absorption. The role of P-gp is to actively secrete absorbed drugs back into the intestinal lumen. After uptake by the enterocyte, the drugs are either metabolized by CYP3A4 or pumped back out (effluxed) into the lumen by the P-gp transporter. Therefore, inhibition of CYP3A4 or P-gp will increase blood levels of the drug

substrate. Some evidence suggests that active grapefruit components may inhibit intestinal P-gp.[19]

A commonly consumed volume (300 ml) of grapefruit juice produced a diminution of oral bioavailability of the drug probes to sufficient magnitude to be pertinent clinically, potentially resulting in reduced benefit of drug.[3, 17]



10.Onset, duration and magnitude of effect of grapefruit juice on inhibition of CYP3A4 enzymes

Furanocoumarins are found predominantly in the grapefruit flesh followed by the sac, peel, and seed. The onset of the interaction can occur within 30 minutes following intake of a single glass of grapefruit juice, and the inhibition can last up to 3 days following the last administration of grapefruit juice. The magnitude of inhibition of CYP isoenzymes by grapefruit components appears to be greatest for CYP3A4 and less significant for other CYP isoforms (eg, 1A2, 2C9, and 2C19). Additionally, the interaction appears to affect CYP3A4 in the gut wall to a much greater extent than in the liver.[20]

A usual single exposure to grapefruit juice appears to impair the enteric, but not the hepatic component of presystemic extraction of oral midazolam. The time course of recovery from CYP3A4 inhibition after a single exposure to grapefruit juice is not clearly established. Recovery is largely complete within three days, consistent with enzyme regeneration after mechanism-based inhibition. 6'7'-dihydroxybergamottin was verified as a potent mechanism-based inhibitor of some drugs by CYP3A *in vitro*.[21]

Concomitant intake of high amounts of grapefruit juice and the CYP3A4 substrate simvastatin increased the Cmax and AUC(0-∞) of simvastatin and simvastatin acid about 5- to 15-fold. When simvastatin is taken 24 hours after ingestion of grapefruit juice, the extent of the interaction is about 90% smaller than during concomitant administration of simvastatin and grapefruit juice. The interaction potential of even high amounts of grapefruit juice with CYP3A4 substrates dissipates within 3 to 7 days after the last dose of grapefruit juice.[22]

Other similar fruits and herbal products which can cause the drug interactions

Seville orange: Seville orange juice is not usually consumed as a juice because of its sour taste, but it is found in marmalade and other jams.[7] When a study was conducted to determine whether Seville orange juice produces a grapefruit juice–like interaction with felodipine and whether bergamottin, DHB, or other furocoumarins are involved. The results suggested that, Seville orange juice and grapefruit juice interact with felodipine by a common mechanism, which is probably inactivation of intestinal CYP3A4.Bergamottin and DHB may be "marker substances" in foods for this interaction. The lack of interaction between Seville orange juice and cyclosporine suggests that grapefruit juice may also inhibit intestinal P-gp, whereas Seville orange juice may selectively "knock out" intestinal CYP3A4.[9,10] Lime juice was reported to increase felodipine serum conc. In some people.Wheather lemon juice interacts with drug is unknown.

Red wine: Like grapefruit juice, red wine also contains a complex mixture of molecules including flavonoids and other polyphenols. These electron rich molecules are likely substrates for CYP3A4 and may also inhibit the enzyme.

Table 1: Possible interactions between grapefruit juice (GJ)* and drugs metabolized by CYP3A4.[14]

Drug Class	Drug	Possible Adverse Effects	Increased Oral Bioavailability	Management
Antiarrhythmics	Amiodarone Quinidine	Arrhythmias None	Yes No	Avoid GJ None
Antibiotics	Clarithromy Cin	None	No	None
Antihistamines	Terfenadine	Arrhythmias, prolonged Q-T interval	Yes	Avoid GJ
Anxiolytics	Buspirone Diazepam Midazolam Triazolam	Decreased psychomotor performance Increased Seditation “ “	Yes Yes Yes Yes	Avoid GJ Avoid GJ Avoid GJ Avoid GJ
Calcium channel blockers	Amlodipine Felodipine Nifedipine Nimodipine Diltiazem Verapamil	Tachycardia, Hypotension “ “ “ None None	Yes Yes Yes Yes No No	Avoid GJ Avoid GJ Avoid GJ Avoid GJ None None
Corticosteroids	Ethynil estradiol Progesterone Prednisome	Unknown Unknown None	Yes Possible No	Monitor for side effects Monitor for side effects None
HMG COA reductase inhibitors	Atorvastatin Cerivastatin Lovastatin	Myopathy, Headache, Rhabdomyolsis “ “	Yes Possible Yes	Avoid GJ Monitor for side effects Avoid GJ

	Pravastatin Simvastatin	“ “	Yes Yes	Avoid GJ Avoid GJ
HIV protease inhibitors	Saquinavir	Unknown	Yes	Monitor for side effects
Immunosupressants	Cyclosporine	Renal/hepatic dysfunction, increased	Yes	Avoid GJ
Neuropsychiatrics	Carbamazepine Phenytoin	Drowsiness, Respiratory depression None	Yes No	Avoid GJ None
Other	Carvedilol Theophylline	Bradycardia, hypotension None	Possible No	Monitor for side effects None

11. Grapefruit juice and drug interactions

Benzodiazepines

Many benzodiazepines, including midazolam and triazolam, are substrates of CYP3A4 and are metabolized by hepatic and intestinal CYP3A4. Coadministration with grapefruit juice did not alter the pharmacokinetics and pharmacodynamics of intravenous midazolam. After an oral dose of midazolam, however, grapefruit juice significantly increased the peak plasma concentration by 56% and the area under the curve (AUC) by 52%.[26] These changes were associated with significant alterations in the pharmacodynamic effects of midazolam, such as delay of the reaction time. Additionally, grapefruit juice increased the AUC (by 50%) and the peak plasma concentration (by 30%) of triazolam in healthy volunteers and was associated with increased drowsiness. Caution must be taken when giving oral midazolam, particularly in patients with other causes for increases in midazolam bioavailability, such as advanced age, liver cirrhosis, and coadministration of other CYP3A4 inhibitors. All of these conditions may potentiate the effects of grapefruit juice.[31,32]

Immunosuppressants

Cyclosporine is an immunosuppressant used widely in solid organ and bone marrow transplantation as well as in the treatment of psoriasis. Oral cyclosporine formulations (ie, oil/water and microemulsion) have been well documented to interact with grapefruit juice through inhibition of CYP3A4 and P-gp. However, intravenous cyclosporine formulations do not interact. In one study, the mean absolute oral bioavailability of cyclosporine increased by 62% with grapefruit juice administration, but there was no significant effect with intravenous

cyclosporine.[33] The magnitude of pharmacokinetic changes associated with the grapefruitcyclosporine interaction is variable and unpredictable within individuals and should not be used as a strategy to reduce cyclosporine dosages and save on drug costs.

Tacrolimus is an immunosuppressant metabolized by CYP3A4. Because the bioavailability of tacrolimus is doubled by ketoconazole, a potent CYP3A4 inhibitor, an interaction with grapefruit juice may also occur. Until more data are available, concurrent administration of tacrolimus and grapefruit juice should be avoided.

Calcium channel blockers

The dihydropyridine calcium channel blockers, felodipine, nifedipine, nisoldipine, and nitrendipine, are substrates of CYP3A4 and undergo extensive first-pass metabolism by hepatic and intestinal CYP3A4. When grapefruit juice is administered in combination with oral felodipine, concentrations of felodipine increase significantly compared with felodipine alone. When felodipine was administered intravenously with oral grapefruit juice, the plasma concentration of felodipine was not significantly altered. Clinical data show that the ingestion of 1 glass of grapefruit juice can alter felodipine pharmacokinetics for up to 3 days. Thus, when dosing a patient who has been on grapefruit juice, a 3-day washout period should occur before initiating felodipine.

Verapamil, a nondihydropyridine calcium channel blocker, is commonly used for the treatment of cardiovascular conditions and migraines. In healthy volunteers, administration of verapamil 120 mg twice daily for 3 days plus grapefruit juice 200 mL twice daily for 5 days resulted in a moderate but statistically significant increase in verapamil concentrations. In this study group of healthy volunteers, changes in heart rate or blood pressure were not statistically significant and the combination of grapefruit juice and verapamil should be avoided.[34,35]

HMG-CoA Reductase Inhibitors (Statins)

A study showed that 2 days of pretreatment with 200 mL doublestrength grapefruit juice 3 times a day, as compared with water, prior to administration of lovastatin 80 mg increased the peak concentrations of lovastatin and the metabolite, lovastatin acid, by 12- and 4-fold, respectively. The AUC for lovastatin and the metabolite also increased significantly, 15- and 5-fold, respectively. The half-life remained unchanged. In another study, 8 oz (240 mL) of regular- strength grapefruit juice was administered in the morning, 12 hours after

pretreatment with lovastatin 40 mg once daily for 3 days. Plasma concentrations of lovastatin increased by approximately 30%.[36]The inconsistent results of these 2 studies are most likely due to differences in lovastatin dosage, pretreatment regimens, and grapefruit juice potency.

Administration of a single dose of simvastatin 60 mg after 2 days of pretreatment with 200 mL of doublestrength grapefruit juice administered 3 times daily resulted in a 9- and 7-fold increase in serum concentrations for simvastatin and the metabolite, simvastatin acid.The AUC was increased 16- and 7-fold for simvastatin and simvastatin acid, respectively.

Pretreatment with 200 mL doublestrength grapefruit juice 3 times a day for 2 days resulted a 2.5-fold increase in the AUC of atorvastatin 40 mg. In addition, the half-life of atorvastatin was increased from 7.8 hours to 13.3 hours. The AUC of atorvastatin's active metabolites, atorvastatin lactone and 2-hydroxyatorvastatin, are increased approximately 1.3-fold. In a similar study, grapefruit juice had no effect on pravastatin (40 mg) serum concentration or AUC.

The results of these studies suggest that concomitant administration of grapefruit juice with atorvastatin, lovastatin, and simvastatin should be avoided. Potentially serious adverse reactions due to elevated levels of statins and metabolites include myalgia and rhabdomyolysis. If this combination cannot be avoided, pharmacists should educate patients on the symptoms of statin-induced myalgia and rhabdomyolysis (eg, muscle aches, back pain). A safer alternative would be pravastatin. Fluvastatin is not metabolized by CYP3A4 and should not interact, although it has yet to be studied with grapefruit juice.[36]

Anti infective agents

Amprenavir

Twelve healthy volunteers (6 male, 6 female) took single 1200 mg doses of the protease inhibitor amprenavir with either 200 mL of water or unknown-strength GJ in a randomized crossover fashion. Cmax was decreased 22%, and total AUC was decreased 11% with GJ, while time to peak concentration changed from 45 minutes to 67 minutes with GJ (50% increase). Pharmacokinetic curves with or without GJ were essentially superimposable, and the authors concluded that the effect of GJ on amprenavir was not clinically significant, and approximately equivalent to the minor effects seen on amprenavir pharmacokinetics seen with food intake.[38]

Clarithromycin

Twelve healthy male subjects were given either 240 mL water or single-strength GJ before and after a single dose of clarithromycin in a randomized crossover study. Administration of GJ increased the time to peak concentration of clarithromycin and its 14-hydroxy metabolite, but did not otherwise affect pharmacokinetic parameters. The authors concluded that clarithromycin can safely be consumed with GJ without concern that the drugs antimicrobial activity may be altered, due to a pharmacokinetic interaction.[37]

Miscellaneous drugs

Budesonide

After extensive intake of grapefruit juice (observed in male subjects taking in 600 mL of concentrated grapefruit juice per day for 4 days), the systemic exposure for oral budesonide increased approximately 2-fold. As with other drugs primarily being metabolized through CYP3A, regular ingestion of grapefruit or its juice, should be avoided in connection with budesonide administration.[34]

Psychiatric drugs

Buspirone

Ten healthy volunteers (4 male, 6 female) received buspirone 10 mg after 2 days of either 200 mL double-strength GJ taken three times daily or water. AUC was increased by a mean of 821%, and Cmax was increased by a mean of 329%. Time to peak concentration was prolonged significantly in the GJ group, from 45 minutes to 180 minutes. Half-life was also increased by 50% in the GJ group. Mild side effects including dizziness, nausea, drowsiness and tingling were reported in 8 volunteers in the GJ phase, and 7 volunteers in the water phase. No effect was seen on psychological tests, such as the digit symbol substitution test (DSST) but overall subjective drug effect was perceived to be significantly greater. This is in keeping with the pharmacological profile of buspirone, such that the pharmacodynamic effects are not as well reflected in the classic psychomotor tests as those of benzodiazepines. The authors concluded that although buspirone has a relatively wide therapeutic index, concomitant use of at least large amounts of grapefruit juice with buspirone should be avoided.[39]

The following drugs definitely interact with CYP3A4

Amfebutamone, Wellbutrin (Welbutrin), Paroxetine, paroxetine hydrochloride, Valproate semisodium, divalproex sodium, carbamazepine[24], digoxin[25] buspirone[26] Benzodiazepines, including: alprazolam, diazepam, midazolam, lorazepam, oxazepam, and chlordiazepoxide.

Additional drugs found to be affected by grapefruit juice include

Statins such as atorvastatin,[27] lovastatin,[28,29] and simvastatin. Dihydropyridines including felodipine (Plendil), nicardipine, difedipine, nisoldipine, nitrendipine, losartinrepaglinide, verapamil, Antiarrhythmics including amiodarone, quinidine Cardioquin, disopyramine, propafenone, and carvediol.

The male impotence drugs sildenafil (Viagra), tadalafil and vardenafil. The anti-migrane drugs ergotamine and nimodipine

Probably Non -Interacting drugs

The following drugs, at least when not interacting with other drugs, are probably safe when consumed withgrapefruits: Lamotrigine.

12.Management of Grapefruit-Drug Interactions

Grapefruit is a healthy addition to a well-balanced diet. However, the fruit has been shown to affect the metabolism of many medications, increasing the risk of toxicity and adverse effects. Characteristics of oral medications that may interact with grapefruit include extensive metabolism through the intestinal cytochrome P450 3A4 system, low bioavailability, and a narrow therapeutic index. Prominent medications known to interact with grapefruit include statins, antiarrhythmic agents, immunosuppressive agents, and calcium channel blockers. There are equally effective alternatives to these drug classes that do not have the potential to interact with grapefruit. These alternative drugs may be substituted if a patient experiences or is at risk of a grapefruit-drug interaction. Patients also may choose to exclude grapefruit from their diets and consume other fruits, including other types of citrus, to avoid an interaction.

Grapefruit is a citrus fruit that is low in calories; rich in vitamin C, potassium, and dietary fiber; and has been a recommended fruit of the American Heart Association's "Healthy Heart Campaign."[41] The authors of a study that used grapefruit juice to mask the taste of ethanol inadvertently discovered an interaction between grapefruit and the calcium channel blocker

felodipine (Plendil). They observed that patients who consumed grapefruit juice had felodipine plasma concentrations two to three times higher than normal levels.

KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References	Comments
Patients should discontinue grapefruit consumption for 72 hours before use of a drug that may interact with it.	C	43	The potential for a grapefruit-drug interaction persists for up to 72 hours according to one study.
Potential grapefruit-drug interactions cannot be avoided by separating times of medication administration and grapefruit consumption.	C	**43**	Studies have shown that consuming 8 oz of grapefruit juice may decrease the concentration of intestinal cytochrome P450 3A4 by 47 percent for 24 to 72 hours.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system.

The discovery of this and other clinically significant interactions may have caused health care professionals to hesitate before universally recommending grapefruit as part of a healthy diet. Because grapefruit-drug interactions exist, strategies should be devised to manage potential interactions. A patient may choose to exclude grapefruit from his or her diet and substitute other fruits, including any other citrus.[42] However, if the patient wishes to continue to consume grapefruit products, an alternate medication that does not have the potential to interact with grapefruit may be prescribed.

MANAGEMENT

When considering how to manage grapefruit-drug interactions, a physician should first decide if the interaction is clinically relevant. A number of medications (e.g., angiotensin receptor blockers, buspirone [BuSpar], estrogens, fexofenadine [Allegra], itraconazole [Sporanox], sildenafil [Viagra], triazolam [Halcion], warfarin [Coumadin]) reportedly or theoretically interact with grapefruit. However, many of these interactions have not been proven clinically significant, or inconsistent data exist.Tabledescribes medication classes that have had

documented, clinically significant interactions with grapefruit products, and possible alternative therapies for these drug.

Table-2: 1 Grapefruit-Drug Interactions and Alternative Therapies[45,46,47]

Drug Class	Drugs Potentially affected by grapefruit	Effect of Interaction	Alternative Treatments
Antiarrhythmics	Amiodarone (Cordarone), disopyramide (Norpace), quionidine	Increased plasma concentrations of amiodarone may cause thyroid or pulmonary toxicity, liver injury, QTc prolongation, proarrhythmic disorders, and bradycardia, Increased plasma concentration of quinidine and disopyramide may be cardiotoxic causing torsadesdepointes	Digoxin (Lanoxin), diltiazem (Cardizem), Verapamil (Calan) Beta blockers
Calcium channel blockers	Felodipine (Plendil), Nicardipine (Cardene), nifedipine (Procardia), nimodipine (Nimotop), nisoldipine (Sular)	Increased plasma concentration may lead to flushing, peripheral edema, headaches, tachycardia, Symptomatic hypotension, and myocardial infraction in rare cases.	Amlodipine (Norvasc), diltiazem (Cardizem), verapamil (Calan)
Statins	Atorvastatin (Lipitor), lovastatin (Mevacor), simvastatin (Zocor)	Increased plasma Fluvastatin concentration may (Lescol) cause headaches, Pravastatin gastrointestinal complaints, hepaticrosuvastanin inflammation, and (Crestor) myopathies (e.g., rhabdomyolysis.)	Fibric acids nicotinic acid, or bile acid sequestrants
Immunosuppressants	Cyclosporine (Sandimmune, Neoral), tacrolimus (Prograf)	Increased drug exposure without effects on peak concentration may cause increased adverse events or toxicity evidenced by renal toxicity, hepatic toxicity, and increased immunosuppression.	No alternatives Available
Protease inhibitors	Saquinavir (Fortovase)	Increased plasma concentrations may cause increased side effects such as headache, fatigue, insomnia, and anxiety.	Amprenavir (Agenerase), atazanavir (Reyataz), fosamprenavir (Lexiva), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir)

The importance of clearly understanding possible interactions between drugs and grapefruit products is becoming more evident. The manufacturers of cyclosporine(Sandimmune, Neoral) and simvastatin (Zocor) have gone so far as to place warnings on their drugs' package inserts.[48]

13.CONCLUSION

A glass of grapefruit juice has the potential to augment the oral bioavailability and to enhance the beneficial or adverse effect of a broad range of medication, even the juice consumed hours before. The grapefruit juice acts by inhibiting presystemic drug metabolism mediated by CYP3A4 isoform in small bowel.

Considering how to manage grapefruit drug interactions, a pharmacist should be competent enough to decide whether the interaction is clinically relevant. A number of medications are reported to have interactions with grapefruit. However many of the other medications have not been proven clinically significant to have interaction. The importance of clearly understanding possible interactions with grapefruit products is becoming more evident. The physicians, pharmacists and other health professionals should educate patients about consumption of grapefruit juice with medication.

When thinking of substitute for grapefruit juice, there are several other fruit juices available including orange juice as a first choice.

The recent studies on recovery of the intestinal CYP3A4 enzymes after consuming grapefruit juice suggest that during the clinical trials and pharmacokinetic studies, grapefruit juice should be avoided at least for 72 hours rather than 48 hours or less so that possible inter-subject variability in pharmacokinetic parameters can be reduced.[30]

In addition, it is recommended that drugs possibly interacting with grapefruit juice should be appropriately labeled.

The serendipitous observation of increased plasma felodipine concentration by grapefruit juice, provided fundamental new knowledge to stimulate further researches required to understand the interactions of GJ with medications and to determine amount of GJ considered safe for administration with drugs and with different patient populations.

14. REFERENCES

1. Shiew-Mei Huang, Stephen D. Hall, Paul Watkins, Lori A. Love, CosetteSerabjit-Singh, Joseph M. Betz, Freddie Ann Hoffman, Peter Honig, Paul M. Coates, Jonca Bull, Shaw T. Chen, Gregory L. Kearns, and Michael D. Murray, Drug interactions with herbal products and grapefruit juice: A conference report, *ClinPharmacolTher,* 2004; 75: 1-12.

2. J. David Spence, Drug interactions with grapefruit: Whose responsibility is it to warn the public?,*ClinPharmacolTher*, 1997; 61: 395-400.
3. George K. Dresser, David G. Bailey, Brenda F. Leake, Ute I. Schwarz, Paul A. Dawson, David J. Freeman, and Richard B. Kim, Fruit juices inhibit organic anion transporting polypeptide–mediated drug uptake to decrease the oral availability of fexofenadine, *ClinPharmacolTher*, 2002; 71: 11-20.
4. David G. Bailey, John H. Kreefk, Claudio Munoz, David J. Freeman, and John R Bend, Grapefruit juice-felodipine interaction: Effect of naringin and 6',7'-dihydroxybergamottin in humans, *ClinPharmacolTher*, 1998; 64: 248-56.
5. David J. Edwards, Michael E. Fitzsimmons, Erin G. Schuetz, Kazuto Yasuda, Murray P. Ducharme, Lawrence H. Warbasse, Patrick M. Woster, John D. Schuetz, and Paul Watkins, 6',7'-Dihydroxybergamottin in grapefruit juice and Seville orange juice: Effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein, *ClinPharmacol Ther*,1999; 65: 237-44.
6. Hugo H. T. Kupferschmidt, HuyRiem Ha, Walter H. Ziegler, Peter J. Meier, and Stephan Krtienbti, Interaction between grapefruit juice and midazolam in humans, *ClinPharmacolTher*, 1995; 58: 20-8.
7. MarikaPasternyk Di Marco, David J. Edwards, Irving W. Wainer, Murray P. Ducharme, The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: The role of gut CYP3A and P-glycoprotein *Life Sciences*, 2002; 71: 1149–1160
8. Theunis C. Goosen, DoréCillié, David G. Bailey, Chongwoo Yu, Kan He, Paul F. Hollenberg, Patrick M. Woster, Lucinda Cohen, J. Andrew Williams, MalieRheeders, Bergamottin contribution to the grapefruit juice–felodipine interaction and disposition in humans, *ClinPharmacolTher*, 2004; 76: 607-17.
9. Shefali M. Kakar, Mary F. Paine, Paul W. Stewart, and Paul B. Watkins, 6'7'-Dihydroxybergamottin contributes to the grapefruit juice effect, *ClinPharmacolTher*, 2004; 75: 569-79.
10. ShefaliMalhotra, BS, David G. Bailey, Mary F. Paine, and Paul B. Watkins, Seville orange juice-felodipine interaction: Comparison with dilute grapefruit juice and involvement of furocoumarins, *ClinPharmacolTher*, 2001; 69: 14-23.
11. K. Fukuda, LianqingGuoa, Noriko Ohashib, Masayoshi Yoshikawab, Yasushi Yamazoe J., Amounts and variation in grapefruit juice of the main components causing grapefruit–drug interaction, *Chromatogr*. B, 2000; 741: 195–203.

12. Antifungal Drug InteractionsContent Director: Russell E. Lewis, Pharm.D. Retrieved on Jan 23, 2010.
13. BararF.S.K."Essential of pharmacotherapeutics",EleventhEdn,byS.Chand and company Ltd, 2006; 43.
14. Journal of food science, 2007; 72A, S261-62.
15. Bailey DG, Spence JD, Edgar B, Bayliff CD, Arnold JM. "Ethanol enhances the hemodynamic effects of felodipine". *Clin Invest Med*, December 1989; 12(6): 357–62.
16. Hugo H. T. Kupferschmidt, HuyRiem Ha, Walter H. Ziegler, Peter J. Meier, and Stephan Krtienbti, Interaction between grapefruit juice and midazolam in humans.
17. Kerry E. Culm-Merdek, Lisa L. von Moltke, Lu Gan, Kelly A. Horan, Robyn Reynolds, Jerold S. Harmatz, Michael H. Court, and David J. Greenblatt, Effect of extended exposure to grapefruit juice on cytochrome P450 3A activity in humans: Comparison with ritonavir, *ClinPharmacolTher*, 2006; 79: 243-54.
18. Jari J. Lilja, Janne T. Backman, JoukoLaitila, HarriLuurila, and Pertti J. Neuvonen, Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol, *ClinPharmacolTher*, 2003; 73: 192-8.
19. Ute I. Schwarz, Diana Seemann, ReinhardOertel, Stephan Miehlke, EberhardKuhlisch, Martin F. Fromm, Richard B. Kim, David G. Bailey, and Wilhelm Kirch, Grapefruit juice ingestion significantly reduces talinolol bioavailability, *ClinPharmacolTher*, 2005; 77: 291-301.
20. Mary F. Paine, Anne B. Criss, and Paul B. Watkins, Two Major Grapefruit Juice Components Differ in Time to Onset of Intestinal CYP3A4 Inhibition, *The Journal Of Pharmacology And Experimental Therapeutic*, 2005; 312: 1151–1160.
21. David J. Greenblatt, Lisa L. von Moltke, Jerold S. Harmatz, Gengsheng Chen, James L. Weemhoff, Cheng Jen, Charles J. Kelley, Barbara W. LeDuc, and Miguel A. Zinny, Time course of recovery of cytochrome P450 3A function after single doses of grapefruit juice, *ClinPharmacolTher*, 2003; 74: 121-9.
22. Jari J. Lilja, Kari T. Kivistö, and Pertti J. Neuvonen, Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin, *ClinPharmacolTher*, 2000; 68: 384-90.
23. AnasSaadeddin, Francisca Torres-Molina, Jaime Cárcel-Trullols, AmparoAraico, José Esteban Peris, Effect of cytochrome P450 inhibitors (diethyl dithiocarbamate, ketoconazole and grapefruit juice) on the pharmacokinetics of all-trans-retinoic acid, *Il Farmaco*, 2004; 59: 697–702.

24. Santosh K. Garg, Naresh Kumar, Vinod R Bhargava, and Sudesh K. Prabhakar, Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy, *ClinPharmacolTher,* 1998; 64: 286-8.
25. Laurent Becquemont, C&lineVerstuyft, Reinhold Kerb, Ulrich Brinkmann, Martine Lebot, Patrice Jaillon, and Christian Funck-Brentano, Effect of grapefruit juice on digoxin pharmacokinetics in humans, *ClinPharmacolTher,* 2001; 70: 311-6.
26. Jari J. Lilja, Kari T. Kivistii, Janne T. Backman, Tommi S. Lamberg, and Pertti J. Neuvonen, Grapefruit juice substantially increases plasma concentrations of buspirone, *ClinPharmacolTher,* 1998; 64: 655-60.
27. Jari J. Lilja, Kari T. Kivistö, and Pertti J. Neuvonen, Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin, *ClinPharmacolTher,* 1999; 66: 118-27.
28. TeemuKantola, Kari T. Kivistii, and Pertti J. Neuvonen, Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid, *ClinPharmacolTher,* 1998; 63: 397-402.
29. John D. Rogers, Jamie Zhao, Lida Liu, Raju D. Amin, BS, Kathleen D. Gagliano, Arturo G. Porras, Robert A. Blum, Michael F. Wilson, Michael Stepanavage, and Jose M. Vega, Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, *ClinPharmacolTher,* 1999; 66: 358-66.
30. Amyl Stump, Terri Mayo, and Alan Blum, Management of Grapefruit-Drug Interactions, *Am Fam Physician,* 2006; 74: 605-8, 611.
31. Hukkinen SK, Varhe A, Olkkola KT et al. Plasma concentrations of triazolam are increased by concomitant ingestion of grapefruit juice. ClinPharmacolTher, 1995; 58: 127-31.
32. 18. Kupferschmidt HHT, Ha HR, Ziegler WH et al. Interaction between grapefruit juice and midazolam in humans. ClinPharmacolTher, 1995; 58: 20-8.
33. 48. Ducharme MP, Warbasse LH, Edwards DJ et al. Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. ClinPharmacolTher 1995; 57: 485-91.
34. 2. Bailey DG, Spence, JD, Munoz C et al. Interaction of citrus juices with felodipine and nifedipine. Lancet, 1991; 337: 268-9.

35. Josefsson M, Zackrisson A.-L., Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. Eur J ClinPharmacol, 1996, 51: 189-93.
36. Kantola T et al. Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. ClinPharmacolTher, 1998; 63: 397-402.
37. Cheng KL, Nafziger AN, Peloquin CA et al. Effect of Grapefruit Juice on Clarithormycin Pharmacokinetics. Antimicrob Agents Chemother, 1998; 42: 927-9.
38. Demarles D, Gillotin C, Bonaventure-Paci S et al. Single-dose pharmacokinetics of amprenavircoadministered with grapefruit juice. Antimicrob Agents Chemother, 2002 May; 46(5): 1589-90.
39. Lilja JJ, Kivisto KT, Backman JT et al. Grapefruit juice substantially increases plasma concentrations of buspirone. ClinPharmacolTher, 1998 Dec; 64(6): 655-60.
40. Gillis MC ed. Compendium of Pharmaceuticals and Specialties 33rd ed. Ottawa: Canadian Pharmaceutical Association, 2002.
41. American Heart Association. Learn and live. Delicious decisions. Accessed April 12, 2006
42. Bailey DG, Dresser GK, Kreeft JH, Munoz C, Freeman DJ, Bend JR. Grapefruit-felodipine interaction: effect of unprocessed fruit and probable active ingredients. *ClinPharmacolTher*. 2000; 68: 468–77.
43. Takanaga H, Ohnishi A, Murakami H, Matsuo H, Higuchi S, Urae A, et al. Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. *ClinPharmacolTher*, 2000; 67: 201–14.
44. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs*, 2004; 4: 281–97.
45. Libersa CC, Brique SA, Motte KB, Caron JF, Guedon-Moreau LM, Humbert L, et al. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J ClinPharmacol*, 2000; 49: 373–8.
46. Min DI, Ku YM, Geraets DR, Lee H. Effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of quinidine in healthy volunteers. *J ClinPharmacol*, 1996; 36: 469–76.
47. Eagling VA, Profit L, Back DJ. Inhibition of the CYP3A4-mediated metabolism and P-glycoprotein-mediated transport of the HIV-1 protease inhibitor saquinavir by grapefruit juice components. *Br J ClinPharmacol*, 1999; 48: 543–52.

48. Bistrup C, Nielsen FT, Jeppesen UE, Dieperink H. Effect of grapefruit juice on SandimmuneNeoral absorption among stable renal allograft recipients. *Nephrol Dial Transplant*, 2001; 16: 373–7.