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Drug Interactions: Reactions with Grapefruit and Related Citrus Fruits

Kamal Kishore Jha, Arun Kumar, Sachin Kumar, Arun Sharma*, Parkhi Rastogi,

Affiliated to: NKBR College of Pharmacy and Research Center, Meerut- Hapur road phaphunda meerut-245206

ABSTRACT

Many people prefers to take medication with citrus fruit juice especially grape fruit juice because of delicious taste, but grape fruit juice interacts with medication, this is also common with citrus fruit juice. There are a number of factors that are responsible for drug interaction between citrus fruit juice and co administered medication. Citrus juices increase the absorption of some medicines by inhibiting CYP3A4 mediated metabolism or by inhibiting Pgp, this due to some components of citrus fruits. This review article contains the results of drug interaction of the drugs of different categories (antihistamines, cholesterol lowering drugs, psychiatric medications, calcium channel blockers, immunosuppressant drugs) with citrus fruit juice on the basis of clinical trials. And it is suggested to avoid grape fruit/citrus fruit juice at least for 72 hrs after administration of the drug otherwise it will be harmful for the body and may be life threatening.

Keywords: citrus fruit juice, drug interaction, immunosuppresants, grapefruit

1. INTRODUCTION

Effectiveness of the ingested drug diminishes, when drugs and certain foods are taken at the same time as they can interact in such ways that reduce the absorption of food nutrients. Additionally, vitamin and herbal supplements taken with prescribed medication can result in adverse reactions.[27]

*Corresponding author
Arun Sharma
C/O Shri Umesh Sharma,
B-28 Shyam Park Ext.
Sahibabad,Ghaziabad
U.P. INDIA
E-mail: arunsharma_hunk@rediffmail.com

1.1 How foods and drugs can interact:

- The action of a medication can speed up or slow down due to food.
- Impaired absorption of minerals and vitamins in the body.
- Stimulation or suppression of the appetite.
- Drugs may alter how nutrients are used in the body.
- Herbs may interact with anesthetics, beta-blockers, and anticoagulants.

Unexpected or adverse effects can be produced if you are taking medication with foods containing active substances that work against certain medications, the food you eat or the supplements you take could cause the medication to work incorrectly.[8]

A variation in drug response of the co-administered drugs is the result of drug-citrus fruit interactions that is due to the changed systemic exposure. In addition to co-administration of other drugs, concomitant ingestion of dietary supplements or citrus fruit or fruit juice could also alter systemic exposure of drugs, thus leading to adverse drug reactions or loss of efficacy.

1.2 Adverse drug reactions, however, frequently go unnoticed or are misdiagnosed in older people for the following reasons:

- Drug reactions sometimes mimic signs or symptoms of disease (e.g., dementia).
- Symptoms of a drug reaction are thought to be due to health related problem.
- Physical reactions to medication, such as fatigue, falling, or weight loss, are considered as effect of ageing.[23]

1.3 There are many physical signs that may be attributed to an adverse drug reaction. These include:

- Fatigue
- Constipation or diarrhea
- Confusion
- Incontinence
- Frequent falls
- Depression
- Weakness or tremors
- Excess drowsiness or dizziness
- Agitation or anxiety
- Decreased sexual behavior

If a problem develops shortly after a person begins taking medication it is wise to alert a physician immediately.

2. Factors Affecting the Extent of Interaction between Foods and Drugs

The impact of food-drug interactions will depend on the following factors: -

- The drug dosage
- A person's age, size, and state of health.
- When the food is eaten and when the medication is taken.

To avoid drug interaction it is not necessary to avoid drugs or foods. In the case of Tetracycline and dairy products, these should simply be taken at different times, rather than eliminating one or the other from the diet.[2]

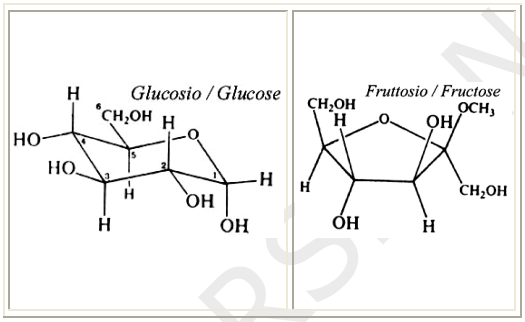
3. Structure of Citrus Fruits[28]

Citrus fruits have a complex structure. Regardless from cultivars, all citrus are similar except for shape and size. Lemons are oblong with major axis from stem to stylar, mandarins tend to be flat (oblate) with the major axis in the equatorial plane, perpendicular to the stem - stylar axis; most oranges tend to be round. Different are, also, sizes usually expressed as equatorial diameter (lemons from 4.4 to 6.4 cm, oranges from 5.7 to 9.5 cm, grapefruits from 9.5 to 14.5 cm). The epidermis of citrus fruits (peel) consists of an epicuticular wax layer in platelets. The fruit surface usually carries an assortment of dead and living fungi and bacteria, particularly if grown in humid climate. Immediately under epidermis is located the flavedo characterized by a green, yellow or orange colour, interspersed oil glands and no vascular bundle. Next layer is the albedo that is composed of loosely packed, many branched, tube-like cells that form a continuous network with the

greatest part of tissue volume comprised of intercellular space. Albedo is very rich in flavonoids, a class of chemicals, which impart a bitter taste to the juice. Next layer is the endocarp, the edible part of the fruit with segments containing juice vesicle. The most internal part is the core made by a spongy tissue similar to the albedo.

4. Chemical Composition Of Citrus Fruits[28]

Carbohydrates represent most of soluble solids in citrus fruits; they are present both as simple sugars and as polysaccharides. Citrus flavor is due to the blend of sugars, acids and specific flavor compounds, some of which are sugar-containing substances known as glycosides. Contribution to fruit colour may be made by sugar-containing anthocyanidins.



Between monosaccharides, major components are glucose and fructose. But fructose and rhamnose are constituents of citrus pectic substances.

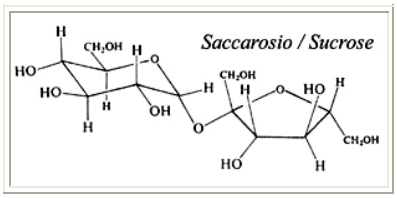
Saccharose is the main naturally occurring oligosaccharide in citrus fruits.

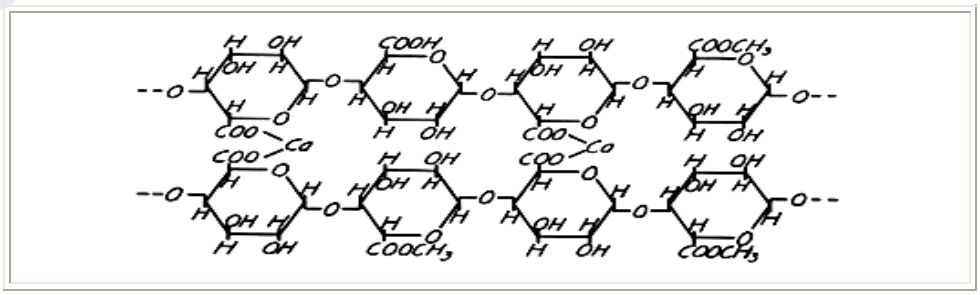
Protopectin*:* the term is applied to the water insoluble parent pectic substance that occurs in plants and which upon restricted hydrolysis yields pectin or pectinic acids.

Pectinic Acids*:* the term is used for colloidal polygalacturonic acids containing more than a negligible portion of methyl ester groups. Pectinic acids, under suitable conditions, are capable of forming gels with sugar and acids or, if suitably low in methoxyl content, with certain metallic ions.

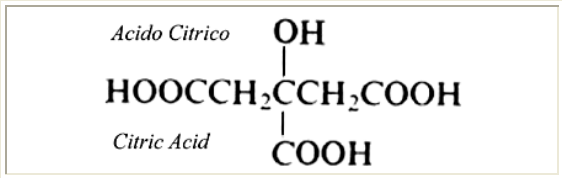
Pectin**:** the term designates those water-soluble pectinic acids of varying methyl ester content and degree of neutralization that are capable of forming gels with sugars and acids under suitable conditions.

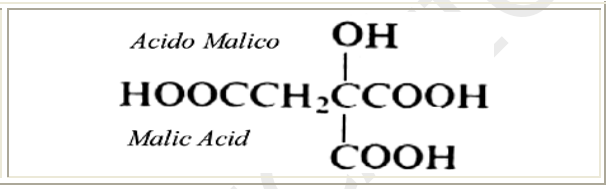
Pectic Acids: the term is applied to pectic substances mostly composed of colloidal polygalacturonic acids and essentially free from methyl ester groups.





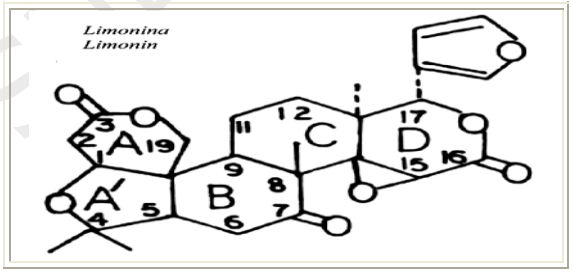
Pectinic acids, the most useful of the pectic substances because of their jellying power, are divided into two groups of pectins for commercial gel making. High-methoxyl (above 7 % methoxyl) will form jams and jellies with the proper proportion of sugar and acids.





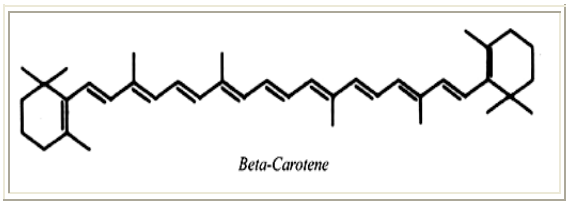
D-Isocitric Acid is contained in small concentration, but is an important quality and purity criteria, whilst Oxalic Acid, Succinic Acid, Malonic Acid, Quinic Acid, Tartaric Acid, Adipic Acid, 2-ketoglutaric Acid are contained just in traces. Total acidity range has an extremely wide range between different species, but also growing area affect acidity.

Nitrogenous Compound in Citrus are contained in rather small concentration but are to be considered important for a correct evaluation of juices purity. Between nitrogenous compounds the most important are free amminoacids that represent about 70 % of total nitrogenous compounds. Nitrogen bases and nucleic acids contents are extremely low.



Citrus lipids can be differentiated in three classes: nonpolar, polar (non ionic) and polar (ionic). Between nonpolar lipids there are aldheydes, ketones and alcohols with long chain, carotins and their esters and some triglycerides. Non ionic polar lipids usually contain sugars like glycosilglycerides. Polar ionic lipids contain reactive functional groups like aminic, carboxylic or phosphoric; free fatty acids and phosphatidic acid belong to this group. Despite their small content, lipids are important because are involved in "off-flavors" development during juices storage. The oil contains 95 % tryglicerides and small amounts of free fatty acids.

Carotenoids derive their name from the main representative of their group, beta-carotene and are pigments widely spread in nature responsible for bright shades ranging from yellow to deep red.



A group of complex substances chemically related triterpene derivatives, has been named limonoids; all components have a furan ring attached to the D-ring at C-17. Between limonoids, the most important citrus constituent is known as lemonin.

Flavonoids are very abundant in Citrus and have a very complex pattern. Three types of flavonoids occur in Citrus: flavanones (including 3-hydroxyflavanones), flavones (including 3-hydroxyflavones) and anthocyanins. Depending upon whether or not a glycosyl residue is present, the flavanones and flavones are further divided in O-glycosyl, aglycones and C-glycosylflavones. Anthocyanins are only known as constituents of blood oranges. The most important flavanones are hesperidin, naringin, poncirin, heriocitrin, neoheriocitrin and neohesperidin. Between flavones, the most important are rhoifolin, rutin and diosmin.

With respect to *vitamins*, the most important is Vitamin C (Ascorbic acid), a glass of orange juice supply 60 & of RDA, other vitamins are : Pholacine, Vitamin B6, Thiamine, Riboflavin, Biotin, Pantotenic acid and products with Vitamin A type activity. Average quantities in freshly sqeezed orange juice are reporten in the following table:

Vitamin	Units/100 ml
Ascorbic Acid	35 – 56 mg
Thiamine	60 – 145mg
Riboflavin	11 – 90mg
Niacin	200 – 300mg
B-6	25 – 80mg
Pholacin	120 – 330mg
Pantotenic Acid	130 – 210mg
Biotin	1 – 3mg
Vitamin A	190 – 400ml

5. Types of Medicines Interact with Grapefruit Juice

Most of the medicines do not interact with grapefruit juice. Interactions between grapefruit juice and the some of the drugs in the following categories has found:

- Drugs used to treat high blood pressure
- "Statin" drugs used to reduce blood cholesterol
- Immunosuppressant drugs used after transplant operations
- Protease inhibitors used to treat HIV/AIDS
- Some anti-anxiety and antihistamine medications.[1]

6. Mechanism of drug interaction with citrus fruits

One mechanism of interaction is thought to be through the inhibition of CYP3A4-mediated metabolism (often first-pass metabolism) by a component of grapefruit juice, which increases concentrations of the affected drug. CYP3A4 is located in both the liver and the enterocytes (small intestine epithelial cells). One study concluded that a mechanism for the effect of grapefruit juice (studied on the felodipine/grapefruit juice interaction) was a selective downregulation of CYP3A4 in the small intestine. There may in fact be a post-transcriptional decrease in the amount of small intestinal CYP3A enzyme rather than a

competitive or non-competitive inhibition of the enzymes.[1, 4, 13, 17]

A second mechanism of interaction is possibly through Pgp. This is located in the apical brush border of the enterocytes. Pgp is a member of the adenosine triphosphate-binding cassette (ABC) superfamily of proteins. The role of the Pgp transporter is to carry lipophilic molecules from the enterocyte back into the intestinal lumen. After uptake by the enterocyte, many lipophilic drugs are either metabolised by CYP3A4 or pumped back into the lumen by the Pgp transporter. Pgp and CYP3A4 may act in tandem as a barrier to oral delivery of many drugs. Inhibition of either or both systems can increase the bioavailability of a drug. *In vivo* data show that grapefruit juice may activate Pgp in intestinal cell monolayers. Therefore if grapefruit juice has this activating effect on Pgp *in vivo*, reducing drug bioavailability might counteract the increased bioavailability seen with inhibition of CYP3A. However, clinical studies with grapefruit and cyclosporin have revealed conflicting evidence, suggesting that there may be *in vivo* inhibition of Pgp. Sweet orange juice does not inhibit CYP3A4. Seville (or bitter) orange juice does inhibit CYP3A4 but, unlike grapefruit juice, does not influence cyclosporin disposition.It is not known whether other drugs which interact with grapefruit juice may also interact with this type of orange juice. Tangelos (a hybrid between grapefruit and tangerine) have not been tested for drug interactions.[13]

7. Examples of drug and citrus fruit interaction

7.1 Interaction of citrus fruit Juice with Antihistamines

The most significant interaction of citrus fruit juice occurred with anithistamines. Do not take grapefruit juice if you are taking terfenadine (seldane) or astemizole (Hismanal) due to the possibility of fatal cardiac arrhythmias. Other non-sedating antihistamines are available which do not appear to interact with grapefruit juice. (e.g., loratidine (Claritin) cetirizine (Reactine) or fexofenadine (Allegra).

The most significant documented grapefruit juice drug interaction occurred with terfenadine (Seldane). To study the effect of grapefruit juice on terfenadine 12 healthy subjects were given terfenadine 60 mg with either water or grapefruit juice, co-administered with terfenadine or delayed by 2 hours.

Results:

- None of the 12 had quantifiable levels when the drug was given with water
- Of subjects who took terfenadine co-administered with grapefruit juice, 100% had quantifiable terfenadine levels.
- Of subjects who delayed grapefruit juice ingestion by 2 hours, 33% had quantifiable levels.
- In the group of subjects which co-administered grapefruit juice and terfenadine, a significant mean prolongation in the QT interval measured by electrocardiogram was demonstrated[17]

7.2 Interaction of citrus fruit Juice with Cholesterol Lowering Drugs

Lovastatin (Mevacor)

Ten healthy subjects were studied in an open randomized crossover trial to determine how grapefruit juice interacts with lovastatin. The subjects drank 200 mL double strength grapefruit juice or water for two days before being given a single 80 mg dose of lovastatin (2-4 times the usual dosage).

Results:

- Peak concentrations of lovastatin and lovastatin acid (an active metabolite) were increased on average 12-fold for lovastatin, and 4-fold for lovastatin acid.
- The area under the curve (AUC) was increased 15-fold for lovastatin and 5-fold for lovastatin acid.
- The half-life of lovastatin and lovastatin acid was not affected.

To keep these results in perspective, the study employed double strength grapefruit juice and higher than normal dosage of lovastatin. However, a 15-fold increase in AUC and a 12-fold increase in peak levels as a result of interaction with grapefruit juice should be of serious concern.[14]

Simvastatin (Zocor)

Ten healthy volunteers received either 200 mL water or double strength grapefruit juice three times daily for 2 days before receiving a single 60mg dose of simvastatin (Note: 3-6x the usual dosage), in a randomized crossover fashion[13]. The clinical trial reported that grapefruit juice increased:

- The simvastatin AUC by 1513%
- The Cmax (Maximum concentration) by 842%
- Simvastatin acid AUC by 577%
- Cmax by 555%

Time to peak concentration of simvastatin was increased from 1 hour to 2.5 hours[15].

Atorvastatin (Lipitor)

Twelve healthy volunteers received either 200 mL water or double strength grapefruit juice three times daily for two days before receiving a single 40 mg dose of atorvastatin with either 200 mL water or grapefruit juice in a randomized crossover fashion. Subjects took an additional 200 mL water or grapefruit juice three times daily on day 4 and 5 as well.[16] The results of clinical trials conducted to determine how grapefruit juice intracts with atorvastatin and provastatin are found as:

Grapefruit juice increased:

- The atorvastatin acid AUC by 2.5 fold
- The peak concentration of atorvastatin acid was not affected
- Time to peak concentration by 200%
- Half-life by 70%

Pravastatin (Pravachol)

Eleven healthy volunteers received either 200 mL water or double strength grapefruit juice three times daily for two days before receiving a single 40mg dose of pravastatin with either 200 mL

water or grapefruit juice in a randomized crossover fashion. Grapefruit juice had no significant effects on the pharmacokinetics of pravastatin, other than the tmax of active HMG Co-A reductase inhibitors was significantly prolonged from 1 hour to 2 hours. The authors concluded that pravastatin is not susceptible to interaction with grapefruit juice and other CYP3A4 inhibitors[16].

7.3 Citrus fruit Juice and Psychiatric Medications

Several psychiatric medications are affected by the metabolism of cytochrome p450 isoenzyme 3A4 (CYP3A4). The bioavailability was affected. A significant increase in pharmacodynamic effects, such as prolonged reaction times was also observed. The interactions could have important implications in patients with other conditions that might increase benzodiazepine bioavailability (e.g. advanced age, liver cirrhosis, concurrent use of other medications that inhibit cytochrome P450). These patients should be observed for increased sedation.

Triazolam(Halcion)

Triazolam AUC was increased 48% and Cmax increased 30% in healthy volunteers given triazolam with grapefruit juice. Drowsiness was significantly increased when triazolam was given concurrently with grapefruit juice[10].

Diazepam (Valium)

Eight healthy subjects were given diazepam 5mg orally with either 250 mL water or grapefruit juice. The mean AUC of diazepam was increased 3.2-fold and the peak concentration was increased 1.5-fold by the grapefruit juice. Grapefruit juice postponed the time to reach peak concentration of diazepam from 1.5 hours to 2.1 hours[22].

7.4 Citrus fruit Juice and Calcium Channel Blockers

Several studies recorded the effect of grapefruit juice on calcium channel blockers. The grapefruit juice seems to affect mainly the dihydropyridine family of calcium-channel blockers. Most studies used healthy persons. It is expected that people with existing hypertension or cardiac condition may be more adversely affected by the grapefruit juice interaction.

The following is a summary of clinical findings on how grapefruit juice affects the bio-availability and side reactions of calcium channel blockers.

Felodipine (Plendil, Renedil)

Felodipine was given with double-strength grapefruit juice to six hypertensive patients[5].

Results:

- Tachycardia
- Decreased diastolic blood pressure
- Felodipine AUC increased by 184%
- An increase in side effects (facial flushing, headache, dizziness) were noted.

Nifedipine (Adalat, Procardia)

Patients taking nifedipine experienced an increase in AUC by 34%.

Amlodipine (Norvasc)

In 12 healthy subjects amlodipine AUC was increased by 16% and patients experienced a slight reduction in diastolic blood pressure when amlodipine was given with single-strength grapefruit juice[17].

Nisoldipine

In 12 patients, nisoldipine AUC was increased by 98% when given with grapefruit juice, and peak concentrations were increased by 406%. There was marked variation within individuals as to how they reacted to the grapefruit juice. Only minor effects on blood pressure and heart rate were noted[18].

Verapamil (Isoptin, Calan)

In a crossover study of 24 volunteers, verapamil and norverapamil AUCs were increased 43% and 28%, while the maximum plasma concentration of verapamil and norverapamil were increased 60% and 32%. Four subjects in the grapefruit juice-verapamil phase had a PR interval prolongation to greater than 0.24 seconds.

Diltiazem (Cardizem, Tiazac)

Nine healthy male subjects received 120mg diltiazem with either 200 mL of water or single-strength grapefruit juice[25].

Results:

- AUC and Cmax were not affected by grapefruit juice.
- Elimination half-life did show a small but significant increase (4.1 hours to 5.1 hours when dilitazem given with grapefruit juice).

7.5 Grapefruit Juice and Immunosuppressant Drugs

Grapefruit juice was found to interact with cyclosporine, a popular transplant medication. The serum concentration of cyclosporine was found to increase when grapefruit juice was co administered with the drug. In fact, some transplant physicians are reported to use grapefruit juice to increase the bioavailability of cyclosporine. Many experts discourage such practice, as it is difficult to control the concentration this way. In 12 kidney transplant patients receiving cyclosporine (Sandimmune, Neoral) and grapefruit juice, the ratio of metabolite AUC to cyclosporine AUC and peak concentrations were increased while trough levels were not significantly changed. Fourteen healthy subjects experienced a 45% increase in AUC and increased maximal plasma concentrations when cyclosporine was given with grapefruit juice[7,9,29].

7.6 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. 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 [19,20].

Also, Seville orange juice has been reported to be a possible inhibitor of CYP3A4 enzymes without affecting P-glycoprotein when taken concomitantly with cyclosporine.

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. Potentially, this inhibition could result in drug interactions. Due to the large consumption of wine world-wide, these interactions could be of great clinical importance.

8. Specific interactions

8.1 Breast cancer link

Eating grapefruit every day could raise the risk of developing breast cancer by almost a third. The Study found that in the test subjects, 50,000 post-menopausal women, eating just a quarter of a grapefruit daily raised the risk by up to 30%. It is believed that the fruit boosts the levels of estrogen, which in turn increases the risk of developing the disease[6].

8.2 Citrus Limonoids May Have Anti-Cancer Effects

Limonoids, found in the skin of citrus fruits, could have significant health benefits, scientists said that limonoids may have anti-cancer effects[2].

Limonoids are compounds found in citrus fruits, usually in the peels. They produce the bitter taste and zesty aroma. Citrus limonoids are present in commercial orange juice at about the same level as vitamin C.

Some researchers think citrus limonoids may be responsible for health effects previously attributed to vitamin C. A Japanese company, Wakayama Prefectual Federation of Agricultural Co-operatives, is making an orange juice with triple the level of limonoid glucosides.

Preliminary research found limonoids could prevent and halt cancer under laboratory conditions. They had anti-cancer effects in animals and prevented the spread of human breast cancer in a cell culture. Scientists are now exploring their use more fully.

The effect in the human body and on other types of cancer has not yet been tested. So far the work has progressed from cells to mice, the researchers reported at the conference. Another team is testing the performance of 12 limonoids in preventing cancer in humans.

9. Distribution of drugs on the basis of extent of interaction:

Medications that should be avoided with grapefruit and citrus fruit		
Amiodarone (Cordarone) Astemizole (Hismanal) Atorvastatin (Lipitor) Budesonide (Entocort) Buspirone (BuSpar) Cerivastatin (Baycol) Cilostazol (Pletal) Cisapride (Propulsid,	Prepulsid) Colchicine Eletriptan (Relpax) Etoposide (Vepesid) Halofantrine (Halfan) Lovastatin (Mevacor) Mifepristone (Mifeprex)	Pimozide (Orap) Quinidine (Quinaglute, Quinidex) Sildenafil (Viagra) Simvastatin (Zocor) Sirolimus (Rapamune) Terfenadine (Seldane) Ziprasidone (Geodon)
Use with grapefruit and citrus fruit with caution		
Albendazole (Albenza) Alfentanil (Alfenta) Alfuzosin (Uroxatral) Almotriptan (Axert) Aprepitant (Emend) Aripiprazole (Abilify) Bupropion (Wellbutrin, Zyban) Carbamazepine (Tegretol) Cinacalcet (Sensipar) Clomipramine (Anafranil) Cyclosporine (Neoral) Darifenacin (Enablex) Delavirdine (Rescriptor) Dextromethorphan Diazepam (Valium) Dofetilide (Tikosyn)	Erythromycin (Eryc, E-mycin,Erythromid, Erybid) Eszopiclone (Lunesta) Felodipine (Renedil, Plendil) Fexofenadine (Allegra) Fluvoxamine (Luvox) Gefitinib (Iressa) Imatinib mesylate (Gleevec/Glivec) Indinavir (Crixivan) Itraconazole (Sporanox) Losartan (Cozaar) Methadone (Dolophine) Methylprednisolone (Medrol) Midazolam (Versed)	Nimodipine (Nimotop) Nisoldipine (Sular) Oxybutynin (Ditropan) Propafenone (Rythmol) Quetiapine fumarate (Seroquel) Quinine Ramelteon (Rozerem) Saquinavir (Invirase) Sertraline (Zoloft) Solifenacin (Vesicare) Tacrolimus (Prograf) Tamoxifen (Nolvadex) Tamsulosin (Flomax) Tolterodine (Detrol) Triazolam (Halcion) Trazodone (Desyrel)
Medications with no significant interaction with grapefruit and citrus fruits		
Acebutolol (Monitan, Sectral) Alprazolam (Xanax) Amlodipine (Norvasc) Amprenavir (Agenerase) Caffeine Carvedilol (Coreg) Clarithromycin (Biaxin) Clozapine (Clozaril) Digoxin (Lanoxin) Diltiazem (Cardizem)	Eplerenone (Inspra) Ethinyl estradiol Fentanyl (Actiq) Haloperidol (Haldol) Lansoprazole (Prevacid) Levothyroxine (Eltroxin,Synthroid) Omeprazole (Losec,Prilosec) Phenytoin (Dilantin)8 Pravastatin (Pravachol)	Prednisone (Deltasone) Scopolamine (Hyoscine) 17-Estradiol Telithromycin (Ketek) Theophylline (Theo-Dur,Uniphyl) Verapamil (Calan, Isoptin,verelan) Warfarin (Coumadin)
Medications considered safe for use with grapefruit		
Cetirizine (Zyrtec, Reactine) Desloratadine (Aerius,Clarinex)	Fluvastatin (Lescol) Loratadine (Claritin)	Praziquantel (Biltricide) Rosuvastatin (Crestor)

10. Conclusion:

When 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. when thinking of substitute for grapefruit juice, there are several other fruit juices available including orange juice as a first choice. Orange juice does not contain responsible components in high concentration, instead containing hesperetin, and may be recommended as a substitute for grapefruit. In 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.

In addition, it is recommended that drugs possibly interacting with grapefruit juice should be appropriately labeled and more studies are needed to clarify interactions involving OTC medications and herbal medications. With further research, it should be possible to eventually harness this drug enhancing effect of grapefruit juice to our advantage. However, at the present time, it would be more prudent to avoid drinking grapefruit juice when taking any medications that utilize cytochrome P450 3A4 isoenzymes for any of the steps in their respective metabolic pathways.

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