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# A NARRATIVE REVIEW ARTICLE ON CLINICAL SIGNIFICANCE OF THE INTERRACTION OF DRUGS WITH GRAPE FRUITJUICE

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## ABSTRACT

The aim of the review is to study the interaction between drugs and grape fruit juice. Grape fruit is a nutrition fruit. Many patient are concerned about the potential for drugs interaction with grape fruit juice. Grape fruit juice interact with many of the drugs produce severe problems. Grape fruit or grape fruit juice can alter enzyme in the body and effect how drugs are changed in the body before eliminated. Grape fruit juice decrease the activity of the cytochrome P450 3A4 enzyme that are responsible for taking down many drugs and toxins. It contains compound known as Furano coumarin that block CYP3A4 enzymes (CYP3A4 enzyme inhibition) which in turn affect s the metabolism of the drugs by this enzyme. Blood levels of the drug may rise, resulting in a risk for new or worsened side effects. The literature shows that one whole fruit or 200 milliliters of grape fruit juice can block the CYP3A4 enzyme and leads to drug toxicity metabolized by this enzyme. The review is done to analyze the alteration in clinical significance, class of drugs and the pharmacokinetic properties of drugs due to the interaction with the grape fruit juice. Therefore it is highly importa nt to know the effect of grape fruit juice on the pharmacokinetic properties of the drugs involved. The same information can be shared and highlight it importance while prescribing the drugs among the healthcare professionals specially the prescriber and t he public health promoting safe effective and rational use of drugs in the society.

**KEYWORDS:** Drugs, interaction, grapefruit juice, CYP3A4, pharmacokinetics.

## INTRODUCTION

Drug interaction is a reaction between two or more drugs or between a drug and a food beverage or supplement. Taking a drug for a medical condition can also cause drug interaction.

## TYPES

- Drug-drug interaction
- Drug-food interaction
- Drug-alcohol interaction
- Drug-dieases interaction

Drug food interaction : when food or beverage intake alters a drug s effect if some one taking cholesterol drinks a lot of grape fruit juice this can cause too much of drug to stay in the body this may increased their risk for liver damage or kidney failure Examples of common medications that interact with grapefruit juice include certain statin cholesterol drugs such as atorvastatin (Lipitor), lovastatin, simvastatin (Zocor), felodipine (Plendil) and other calcium channel blockers, clarithromycin (Biaxin), and loratadine (Claritin). Some immunosuppressants have been reported to cause kidney damage, and certain pain medications when mixed with grapefruit juice may be linked with depressed breathing.

Drugs or toxins are usually broken down (metabolized) so that they can be eliminated from the body. Grapefruit or grapefruit juice can alter enzymes in the body and affect how drugs are changed in the body before they are eliminated.

- Grapefruit juice decreases the activity of the cytochrome P450 3A4 (CYP3A4) enzymes that are responsible for breaking down many drugs and toxins.
- Grapefruit contains compounds known as furanocoumarins that block the CYP3A4 enzymes. When grapefruit juice is consumed, the enzyme's ability to break down the drug for elimination is decreased.
- Blood levels of the drug may rise, resulting in a risk for new or worsened side effects.
- One whole fruit or 200 milliliters of grapefruit juice (a bit less than one cup) can block the CYP3A4 enzymes and lead to toxic blood levels of the drug.[1]

Colored (pink and red) grapefruit pulp contains lower amounts of the furanocoumarin derivatives that cause pharmacokinetic interactions than white grapefruit pulp. However, few studies have examined interactions with colored juice products. Therefore, we examined the potential interactions of both white and colored grapefruit products by measuring the concentrations of furanocoumarin derivatives and inhibition of the metabolizing cytochrome P450 (CYP) 3A enzymes, the target of the furanocoumarins. We measured concentrations of three major furanocoumarin derivatives, bergaptol, bergamottin, and 60,70-dihydroxybergamottin, with high-performance liquid chromatography in 21 brands of grapefruit juice sold in Japan, including 14 white and 7 colored brands. Thus, colored grapefruit juice may produce drug interactions at the same rate as white grapefruit juice.[2]

**Active grapefruit components**

Furocoumarins are components of grapefruit juice that may be clinically active. They are highly lipophilic and are present largely in the solid fragments of grapefruit juice. The most prominent furocoumarins are bergamottin and 6',7'- dihydroxybergamottin. Grapefruit juice contains approximately 25 micromol/L of bergamottin; a higher drug interaction was produced when bergamottin was concentrated in the juice.11 Lime juice has a higher bergamottin concentration than grapefruit juice (100 micromol/L and almost no 6',7'dihydroxybergamottin), which may indicate a greater degree of interaction. Lime juice interaction has not been studied but the consumption of large amounts of lime juice is not popular at present. The interaction with drugs can result in either competitive inhibition or mechanism-based inactivation. Competitive inhibition occurs when the agent competes with the drug and occupies the active site on the enzyme so that it cannot metabolize the drug. Mechanism-based inactivation occurs when the metabolized agent is an intermediate that reacts with and inactivates the enzyme. The result of this reaction causes proteolysis of the structurally modified enzyme in the cell. In vitro studies show that the juices of grapefruit and lime inhibit CYP3A4 action in more than one way and that bergamottin is a reversible inhibitor of CYP3A4.11 However, derivatives of the 6',7'-dihydroxybergamottin are powerful competitive inhibitors as well as mechanism-based inactivators of CYP3A4. The combined effect of the furanocoumarins and other asyet- unidentified components acting irreversibly may produce the end effects. Naringin, the most prevalent flavonoid found in grapefruit, also has been shown to contribute to drug oxidative inhibition.12 This multiple-component effect complicates the study of food products.[3]

## METHODOLOGY

**Search strategy**

Science direct, Wikipedia, PubMed, journal and books, article from the authors are used for searching the interaction of drugs with grapefruit juice The search strategy included. All ages, all languages all type of trials and studies.

**Search terms**

The search terms included in interaction of drugs with grapefruit juice, prevention of grapefruit juice, mechanism action of grapefruit juice, drug interactions, types of drugs with grapefruit juice, pharmacokinetics action of ADME.

**Review procedure**

The previous systematic reviews of interaction of drugs with grape fruit juice have been found to be heterogeneous studies. As they were conducted in different countries used different definitions and different methods to collect data. we did not try to analysis the data from a statistical view point but the results are summarized according to the type of interaction being a narrative review.

## RESULTS AND DISCUSSION

According to Y.UESAWA et.al. who conducted a comparison of furanocoumarin levels between white and coloured GFJ and measured levels of furanocoumarin derivatives in various brands of GFJ. Bergaptol concentrations in white and colored GFJ have been studied in which the concentration of Bergaptol in white and colored GFJ ranged from 11.0 to 96.0 mM (mean: 48.2, SE: 7.26, n: 14) and from 9.24 to 65.5mM (mean: 30.3, SE: 9.13, n: 7. Bergamottin and 60,70-dihydroxybergamottin are critical for the pharmacokinetic interactions of GFJ at intestinal CYP3A., These furanocoumarin derivatives were present at the same levels in white and colored GFJ, and therefore might have similar interactions with CYP3A. Other studies showed that levels of furanocoumarin derivatives in fruit meat and juice products made from colored grapefruits were lower than in white grapefruits (Fukuda et al. 2000; De Castro et al. 2006). For example, white grapefruit pulp contained 13 mg/g tissue of bergamottin, and red grapefruits contained only a small percent of this concentration (De Castro et al. 2006).Our findings of similar levels in both white and colored GFJ may be due to variability in GFJ brands, which result from differences in the production process. GFJ brands made from colored cultivars may also include.

Furanocoumarin derivatives from the non-pulp tissues.It had been examined the potential interactions of both white and colored grapefruit products by measuring the concentrations of furanocoumarin derivatives causing the inhibition of the metabolizing cytochromeP450 (CYP) 3A enzymes, the target of the furanocoumarins. The measured concentrations of three major furanocoumarin derivatives, bergaptol, bergamottin, and 60,70-dihydroxybergamottin, with high-performance liquid chromatography in 21 brands of grapefruit juice sold in Japan, including 14 white and 7 coloured brands. The mean difference in bergaptol, bergamottin, and 60,70-dihydroxybergamottin concentrations in white grapefruit

juice samples was 1.59, 0.902, and 1.03 times, respectively, the amounts in colored samples. White samples inhibited CYP3A4-mediated testosterone-6b oxidation in human liver microsomes by 1.04 and 0.922 times (whole juice and furanocoumarin, respectively) the inhibition by colored juice. Thus, colored grapefruit juice may produce drug interactions at the same rate as white grapefruit juicc.[2]

Mary F Paine.et.al. studied the effect of citrus juices on the oral pharmacokinetics of felodipine in healthy volunteers.

The felodipine and juice treatments were generally well tolerated. None of the subjects commented on the taste of the FC free GFJ, which, as judged by one of the investigators (MFP), was sweeter and less bitter than the whole GFJ.[4] The few adverse effects spontaneously reported by the subjects included headache (the most frequent), dizziness, and nausea. These are common side effects of felodipine, and they were resolved by the time of the evening meal. The etiology for the headache in some people could also have been caffeine withdrawal. Nevertheless, the number of reports was greatest for GFJ,[5] the number of reports was second-greatest for OJ(6) and least for FC-free GFJ.[7]

The identification of the inhibitory components in GFJ which is responsible for drug interactions has got several advantages. First of all, measurement of these components in GFJ would allow the standardization of juices used in clinical studies or perhaps even of those available to the public. Second, it may be possible to remove these components from the juice to limit safety concerns. Third, the inhibitory components could be used as “marker substances” to identify other foods with interaction potential. Fourth, these components may have commercial value if they could be formulated safely with certain medications to improve oral bioavailability. The furanocoumarin -free GFJ also inhibited CYP3A4 activity in all three systems but to a much lesser extent than did whole juice. Of import is that the FC-free GFJ behaved in a manner similar to that of OJ, whether under coincubation or preincubation conditions. These results supported the hypothesis that furanocoumarins are the major CYP3A4 inhibitors responsible for interactions between GFJ and certain CYP3A4 substrates invivo.The inhibitory effects of both FC-free GFJ and OJ indicated that nonfuranocoumarins (likely flavonoids) were present in sufficient concentrations to inhibit CYP3A4 in the in vitro systems employed.

The current work shows for the first time that furanocoumarins, in aggregate, mediate the interaction between GFJ and the CYP3A4 substrate felodipine in vivo. However, because felodipine is not known to be a substrate for Pglycoprotein or OATP, these observations do not preclude an interaction between the FC-free GFJ and dual CYP3A4/Pglycoprotein or P- glycoprotein/ OATP substrates. If future studies show that the FC-free GFJ does not interact with such dual substrates, then commercialization of an FC-free GFJ could provide an alternative for patients who are taking medications with interaction potential.[4]

JARI J.et. al. found that pharmacokinetics of glibenclamide the time to c max the half life of glibenclamide,and the amount of hydroxyglibenclamide excreted into urine remained unaltered. Grapefruit juice did not change the pharmacokinetics of glibenclamide. The clarithromycin concentrations implied a good compliance blood glucose did not deviate between the phases.

The present study was conducted to investigate the effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. Clarithromycin moderately increased the AUC and Cmax of glibenclamide, but grapefruit juice had no significant effect on its pharmacokinetics. During the clarithromycin phase, the increase in glibenclamide AUC caused by clarithromy cin varied from 10% to 68%. There were no significant differences in the pharmacodynamics of glibenclamide between the phases, probably partly due to the repeated food intake (for safety reasons) during the study days, which probably contributed to the increased variation in the blood glucose concentrations.

The increased Cmax and AUC (0,•) and an unaltered elimination t1/2 of glibenclamide during the clarithromycin phase suggest that clarithromycin affected the pharmacokinetics of glibenclamide mainly during its absorption. Because clarithromycin inhibits Pglycoprotein, the present findings can be explained by a reduced activity of this efflux transporter in the intestinal wall.

In conclusion clarithromycin moderately increased plasma concentrations of glibenclamide, but grapefruit juice did not have any significant effect on its pharmacokinetics. The mechanism of the clarithromycinglibenclamide interaction may be inhibition of P-glycoprotein in the intestinal wall, with the possible contribution of inhibition of CYP3A4. This interaction could be of clinical significance, because elevated glibenclamide concentrations may increase the risk of hypoglycaemia. Concomitant use of clarithromycin with glibenclamide warrants close monitoring of blood glucose.

The study of effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide show that Clarithromycin moderately increased the AUC and Cmax of glibenclamide, but grapefruit juice had no significant effect on its pharmacokinetics.[8]

EDWARDS D.J et.al. found that an increase in CBZ serum concentration after intake of grapefruit juice compared with day 0, although this increase was not statisticallysignificant The CBZ serum concentrations

after the intake of grapefruit juice increased compared with day 0 (6.70 ± 1.23 ug/ml) . After 5 days of administration of the juice, the concentration of CBZ was 7.40 ± 1.21 ug/mL, but did not differ significantly ($F(3,11) = 0.7413$; $p = 0.5473$) compared to day 0. Similar results (7.90 ± 1.10 ug/mL) were obtained after 10 days' administration of grapefruit juice, and these concentrations did not differ significantly ($F(3,11) = 1.1658$; $p = 0.23290$ compared to day 0. We found a tendency for increased serum concentration of CBZ in our patients. In view of the small number of patients, we could not obtain significant differences in the CBZ concentration. Tolerance of the juice was good, no side-effects were reported during the study.

Grapefruit juice is known to inhibit mammalian cytochrome P450 isozymes such as CYP3A4[9] Edwards et al.demonstrated that grapefruit oil and two furanocoumarin constituents (6', 7'-dihydroxy bergamottin and a closely related dimer) caused a dose-dependent fall in CYP3A4 catalytic activity and immunoreactive CYP3A4 concentration[10] Schmiedlin-Ren et al.[11] showed that the reduction in intestinal CYP3A4 concentration is rapid; a 47% decrease occurred in a healthy volunteer within 4 hrs. after consuming grapefruit juice.

The effect of grapefruit juice on the bioavailability of CBZ in patients with epilepsy. Patients involved in the study received 200 mg of carbamazpeine 3 times a day. They were given either grapefruit juice or 300 mL of water with each CBZ dose. Compared with water, grapefruit juice significantly increased the steady peak concentration of CBZ, although no significant effect was found in the time to reach peak plasma concentration. In our study, we demonstrated that grapefruit juice increased serum concentration of CBZ in children with epilepsy. The mean concentration of CBZ increased from 6.68 up to 7.98 ug/mL after 10 days of juice intake.[12]

The grapefruit juice increases the bioavailability and concentration of CBZ in serum by inhibiting CYP3A4 enzymes in the intestine wall, the liver, and probably by other mechanisms. From the clinical practice perspective, grapefruit juice should not be used by carbamazepine treated epileptic patients to avoid unfavorable fluctuations of CBZ concentration, which may result in the presence of concentration-dependent adverse effects of CBZ.

S.P.BODDU et.al.Found that metabolism studies sufficient levels of CYP3A enzymes in the animals used and found that these levels were indeed sufficient for the metabolism of DTZ.As testosterone is specifically a CYP 3A substrate, we were able to demonstrate that there was CYP 3A enzyme in the S9 fraction and these CYP 3A levels were sufficient to metabolize testosterone.Our invitro metabolism study, data demonstrate that GFJ is an inhibitor of CYP3A.DTZ metabolism was decreased when incubated in control rat liver S9 fraction along with testosterone compared to the incubation with DTZ alone. The normal sac studies in the rat have clearly addressed that the alterations in the oral pharmacokinetics of DTZ could be due to changes at the absorption site.

i.e. in the intestine. The extent of inhibition of CYP enzymes, OATP and induction of P-gp depends upon the levels of furanocoumarins and flavanoids in the GFJ, thus influencing systemic drug levels. Since, the efflux of drug from the blood to the intestine is increased by grapefruit juice, there is slow absorption of the drug and hence an increase in Tmax and ultimately leading to a decrease in the Cmax. Thus GFJ does not demonstrate an influence upon simultaneous administration with DTZ, whereas it induces P-gp and may inhibit OATP upon its chronic administration. Future investigations will study the effect of OATP on DTZ, as well as attempting to provide more clarification of these complex interactions.[13]

Although many studies are available on the effect of Grapefruit juice on various drugs, more pharmacogenetic studies are required to have an in depth study on the same. Most of the studies have been conducted on a smaller population which is its limitation. Hence more number of studies are required in order to validate the effect of drug interactions caused by Grapefruit juice.

## CONCLUSION

It is clear evident that Grapefruit juice especially furanocoumarin present in it being the reason for the development of interactions with the drugs involved in the treatment of various diseases. The drugs thar are causing interactions with grapefruit juice are mainly Carbamazepine,. Mainly it inhibits the p-glycoprotein transporter which affects the absorption a pharmacokinetic parameter studied extensively in various studies. A more detailed study is required to establish the same in large population. A scientific validation of the same can be done if the same is done as a pharmacogenetic study thereby the possibility of having a genetic component in establishing the interaction of Cytochrome P450 oxidase enzyme family in the evolvement of drug interactions with grapefruit juice can be established.

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**ABBREVIATION USED**

**CYP3A4:** Cytochrome P450 **GFJ:** grapefruitjuice, **FC:** furanocoumarin, **CBZ:** carbamazepine, **OATP:** Organic anion transporting polypeptides.

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