Original Article

Hidden Sources of Grapefruit in Beverages: Potential Interactions with Immunosuppressant Medications

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Abstract

Purpose: The interaction between grapefruit-containing beverages and immunosuppressants is not well defined in the literature. This study was conducted to investigate possible sources of grapefruit juice or grapefruit extract in common US-manufactured beverages. The goal was to identify those products that might serve as hidden sources of dietary grapefruit intake, increasing a transplant patient's risk for drug interactions.

Methods: A careful review of the ingredients of the 3 largest US beverage manufacturer's product lines was conducted through manufacturer correspondence, product labeling examination, and online nutrition database research. Focus was placed on citrus-flavored soft drinks, teas, and juice products and their impact on a patient's immunosuppressant regimens.

Results: Twenty-three beverages were identified that contained grapefruit. Five did not contain the word "grapefruit" in the product name. In addition to the confirmed grapefruit-containing products, 17 products were identified as possibly containing grapefruit juice or grapefruit extract.

Conclusion: A greater emphasis should be placed upon properly educating patients regarding hidden sources of grapefruit in popular US beverages and the potential for food-drug interactions.

Key Words—drug interaction, grapefruit, immunosuppression

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Grapefruit is an excellent source of vitamins and phytochemicals. Yet, grapefruit has been linked to many significant drug interactions. The well-documented interaction between grapefruit and grapefruit-containing products and certain medications has been attributed to several different potential mechanisms of interaction. The interference of intestinal cytochrome P-450 (CYP 450) enzymes by grapefruit furanocoumarin derivatives is currently accepted as the primary mechanism of interaction.¹ The CYP 450 3A4 enzyme is an isoform of the CYP 450 system. The CYP 450 system is a diverse family of over 60 enzymes that function to catalyze the oxidation of organic substances. Cytochromes are the major enzymes through which drug metabolism and bioactivation processes occur, accounting for nearly 75% of these metabolic reactions. Active chemical

compounds in grapefruit, known as the *furanocoumarins*, are primarily responsible for the CYP 450 3A4 interaction. Furanocoumarin derivatives include bergamottin, bergapten, bergaptol, and 6',7'-dihydroxybergamottin.² Mechanism-based inhibition of CYP 450 3A4 enzymes in the intestine by furanocoumarins results in a complete inactivation of the enzyme. This inhibition of intestinal clearance by CYP3A4 requires de novo restoration of the isoenzyme prior to returning to normal metabolic function.³ With many oral therapeutic agents undergoing first-pass metabolism by CYP 450 3A4, the effects of enzyme inhibition can be significant. Of additional interest is the interference with P-glycoprotein and organic anion transporting peptides by grapefruit bioactive compounds. In contrast to CYP 450 enzyme interference, these mechanisms of interaction are competitive and relatively short-lived.

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Table 1. Immunosuppressant medications that have the potential for significant interactions with grapefruit and grapefruit-containing products⁴⁻¹⁸

Immunosuppressant	Potential mechanism	Pharmacokinetic effect
Cyclosporine	Inhibition of CYP3A4 and P-glycoprotein	Increased cyclosporine exposure; increased AUC ~40%, in some cases up to 186%; increased C _{max} ; decreased clearance
Everolimus	Inhibition of CYP3A4 and P-glycoprotein	Potential for increased everolimus exposure
Sirolimus	Inhibition of CYP3A4 and P-glycoprotein	Potential for increased sirolimus exposure
Tacrolimus	Inhibition of CYP3A4	Increased tacrolimus exposure; increased tacrolimus concentrations

Note: AUC = area under the time concentration curve; C_{max} = maximum concentration.

Many immunosuppressants, including cyclosporine, tacrolimus, sirolimus, and everolimus, are known to interact with grapefruit, and therefore most transplant recipients are at risk for drug-food interactions⁴ (Table 1). In patients receiving immunosuppressants after organ transplant, rejection, medication toxicity, and infections are all possible negative consequences of medication interaction. Subtherapeutic levels of immunosuppressants may result in rejection, and supra-therapeutic levels may result in toxicity or infection.

The most commonly documented immunosuppressant interactions are with grapefruit and cyclosporine⁵⁻¹³ followed by tacrolimus and grapefruit.¹⁴⁻¹⁶ Interactions have occurred in patients consuming products that were not known to contain grapefruit. In a case report, a patient presented with tremors, blurred vision, electrocardiogram changes, acute renal failure, and a tacrolimus level of 55 mg/dL (therapeutic range, 5-15 mg/dL) after eating more than 1.5 kg of orange marmalade prepared with grapefruit.¹⁵ Few articles have described the interaction between beverages containing grapefruit and immunosuppressive medication.^{17,18} In one article, the citrus beverage *Sun Drop* was found to be the cause of increased cyclosporine concentrations and toxicity in a double lung transplant patient. The patient routinely drank an unreported amount of *Sun Drop* with breakfast; *Sun Drop* contains grapefruit juice or bergamottin, a natural furanocoumarin. This citrus beverage increased the patient's cyclosporine concentrations to more than twice the accepted level and caused tremors and fatigue.¹⁷ Furthermore, the cyclosporine levels normalized with avoidance of this product.

Conflicting evidence was reported in a randomized, 4-way crossover study with a 1-week washout period that studied changes in cyclosporine concen-

trations due to citrus sodas.¹⁸ In the study, 12 healthy volunteers received a single oral dose of cyclosporine with 591 mL of *Sun Drop*, *Fresca*, grapefruit juice, or water (control). Each drink was consumed 2 times on the day before and 3 times on the study day. This study found that there was no significant alteration in cyclosporine concentrations. The mean values ranged from $\pm 3\%$ to 11% of the corresponding water value.

The current literature fails to provide a comprehensive list of beverages containing grapefruit or grapefruit juice and, as such, does not allow a pharmacist to educate patients on the possible hidden sources of food-drug interactions. The purpose of this study was to compile a comprehensive list of popular beverages manufactured in the United States that contain or possibly contain grapefruit constituents. This list will provide an additional resource for patient counseling regarding potential food-drug interactions, specifically interactions with immunosuppressant agents.

METHODS

Popular US manufacturers of beverages and their products were identified. Telephone calls were made to each manufacture to identify beverages that contained grapefruit or grapefruit extract. Each manufacturer's Web site was reviewed to identify products that contained grapefruit juice or grapefruit extract in product labeling.¹⁹⁻²¹ Focus was placed on citrus-flavored drinks, teas, and juice products.

Products were defined as containing grapefruit or possibly containing grapefruit. Products that *contained* grapefruit were verifiable or confirmed as containing grapefruit either via a call to the manufacture or acknowledgment in the product labeling. Products that *possibly contained* grapefruit were

Table 2. Products containing grapefruit juice or grapefruit extract

Coca Cola products	Dr. Pepper/7-Up products	Pepsi Cola products
<i>Fanta Grapefruit</i>	<i>Ruby Red Squirrt</i>	<i>Citrus Blast</i>
<i>Fanta Grapefruit Lemon</i>	<i>Squirrt/ Diet Squirrt</i>	<i>IZZE Sparkling Grapefruit</i>
<i>Fanta Grapefruit Lemon-Lime</i>	<i>Sun Drop/ Diet Sun Drop</i>	<i>IZZE Fortified Sparkling Grapefruit</i>
<i>Fanta Grapefruit Pineapple</i>		<i>Ocean Spray Ruby Red Grapefruit Juice Drink</i>
<i>Fanta Grapefruit Raspberry</i>		<i>Season's Harvest Grapefruit Juice Beverage</i>
<i>Fresca/Diet Fresca</i>		<i>Tropicana Pure Premium Golden Grapefruit Juice</i>
<i>Fuze Tangerine Grapefruit</i>		<i>Tropicana Pure Premium Golden Grapefruit Juice Calcium & Vitamin D</i>
<i>Minute Maid Grapefruit Juice</i>		<i>Tropicana Pure Premium Ruby Red Grapefruit Juice</i>
<i>Simply Grapefruit</i>		<i>Tropicana Ruby Red Grapefruit Juice</i>
		<i>Tropicana Ruby Red Grapefruit Juice Drink</i>
		<i>Tropicana White Grapefruit Juice</i>

defined as those that had a listing of citrus flavors or ingredients that were unable to be confirmed or discounted as grapefruit or grapefruit extract.

RESULTS

The beverage product review resulted in several products that contained verifiable amounts of grapefruit or grapefruit extract (Table 2). From the 3 major beverage manufacturers in the United States (Coca Cola, Pepsi Cola, Dr. Pepper/7-Up),¹⁹⁻²¹ 23 beverages were identified that contained grapefruit; of these, 5 did not contain the word "grapefruit" in the product name. In addition to the confirmed grapefruit-containing products, 17 products were identified as possibly containing grapefruit juice or grapefruit extract (Table 3).

DISCUSSION

This study identified beverages that may contain grapefruit via telephone queries and product review. We conducted a thorough product search of popular

beverages produced by US manufacturers and compiled a list of beverages that did contain grapefruit or grapefruit extract and a secondary list of products that potentially contain grapefruit.

One limitation to our literature review is conflicting evidence supporting a clinically significant grapefruit juice-like interaction between immunosuppressants and citrus sodas (that contain grapefruit as a constituent). The published case study of tacrolimus and *SunDrop*¹⁷ appears to indicate that the potential exists for significant interaction, although a controlled pharmacokinetic study¹⁸ failed to support this hypothesis. These conflicting data may be explained by patient variability. There is high individual variability of CYP3A4 content in the general population, and therefore the effect of inhibition may be unpredictable. It may be prudent pharmacy practice to consider every patient as having a strong potential for interaction. Another possible explanation is the duration of consumption of grapefruit. Unfortunately, a comparison between the case report and the

Table 3. Products possibly containing grapefruit juice or grapefruit extract

Coca Cola products	Dr. Pepper/7-Up products	Pepsi Cola products
<i>Canada Dry Citrus Blend</i>	<i>7-Up (multiple flavors)</i>	<i>Lipton Diet Green Tea with Citrus</i>
<i>Full Throttle Citrus Blend</i>	<i>Country Time Lemonade</i>	<i>Propel - Citrus Punch with Calcium</i>
<i>Nestea Citrus Green Tea</i>	<i>Crush (citrus flavors)</i>	<i>Sierra Mist (multiple flavors)</i>
<i>Nestea Grapefruit Honey Green Tea</i>	<i>Orangina</i>	<i>SoBe Energy Citrus Energy</i>
<i>Powerade Citrus Blend</i>	<i>Snapple (citrus tea flavors)</i>	
<i>Vitamin Water Tropical Citrus</i>	<i>Stewart's (citrus flavors)</i>	
	<i>Sunkist (citrus flavors)</i>	

healthy volunteer study is difficult due to the short-term nature of the study and the lack of available information on the quantity of *SunDrop* ingested in the case report. Even though the results of the healthy volunteer study do not support a clinically relevant interaction between the citrus beverages *SunDrop*, *Fresca*, grapefruit juice, and cyclosporine, an effect in the setting of chronic cyclosporine and grapefruit or grapefruit-containing products may occur and should be assessed further. A previous report supports this hypothesis and shows that chronic co-administration of grapefruit and cyclosporine is more likely to result in a significant drug interaction.⁹

Although many patients are counseled on drug-food interactions with grapefruit, these patients may not be counseled on the potential for interactions with grapefruit-containing products. It is easy to advise patients to avoid fresh grapefruit and grapefruit juice, but it is difficult to provide a comprehensive list of grapefruit-containing products. Vague product labeling, difficulty in obtaining ingredient information from the manufacturer, and conflicting information on the Internet add to the confusion. Furthermore, product manufacturers are reluctant to disclose ingredients of popular sodas, which makes it difficult for pharmacists and patients to determine interactions. Products with grapefruit in the product name do not necessarily contain grapefruit juice or grapefruit extract. Many such products contain juice and rely on artificial fruit flavoring for their citrus taste. In contrast, our study identified 5 products that contain grapefruit juice and did not have grapefruit listed in the product name.

Whereas the use of certain classic allergen food products, like peanuts or eggs, is readily disclosed in ingredient listings, more clarity is needed in products containing grapefruit. Proper patient counseling on drug-grapefruit interactions should include a discussion of the potential for interaction posed by the hidden sources of grapefruit in our diets. Emphasis should be placed on the risks of assuming that manufacturers will automatically include grapefruit as an ingredient, if it is indeed in the product.

Based on our review of pertinent scientific literature, we recommend that an increased focus be placed on patient counseling regarding the hidden sources of grapefruit in beverages, especially in patients who chronically ingest the beverages identified in our study. Further testing should be conducted to evaluate how quantity and chronic administration of grapefruit-containing beverages affect the pharmacokinetics and pharmacodynamics of immunosuppressants.

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