



# Fruit Juice Interactions

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In the 15 years since the discovery that grapefruit juice inhibits cytochrome P-450 3A4 (CYP3A4) in the wall of the small intestine, much work has been done to further define interactions with grapefruit juice and, more recently, with other fruit juices.<sup>1</sup> These studies have led to a better understanding of how drugs are metabolized and transported within the body and how natural products can affect these processes.

## Table

### Drugs Known to Interact with Grapefruit Juice

Drug	Approximate Increase in AUC (%)
Amiodarone	50
Atorvastatin	150
Buspirone	800
Carbamazepine	40
Cyclosporine	50
Diazepam	200
Felodipine	225
Halofantrine	180
Lovastatin	1200
Nifedipine	100
Nisoldipine	300
Nitrendipine	130
Saquinavir	100
Simvastatin	1500
Terfenadine	150
Triazolam	140
Verapamil	40

AUC = area under the concentration-time curve.

The Table lists drugs that are susceptible to grapefruit juice–induced inhibition of their first-pass metabolism and that may produce increased toxicity when administered with adequate amounts of grapefruit juice. In addition to being CYP3A4 substrates, each of these drugs has relatively low bioavailability due to high first-pass metabolism. For example, the bioavailability of lovastatin and simvastatin is about 5%, meaning that a dose of lovastatin or simvastatin is about 95% metabolized before it reaches the systemic circulation. This large amount of normally metabolized drug can be systemically available if an inhibitor of CYP3A4, such as grapefruit juice, is present. Increasing a drug's bioavailability from 5% to 10% will increase its area under the concentration-time curve (AUC) by 100%. An increased incidence of side effects and toxicity may occur.

Seville orange juice, a constituent of marmalade, also has been shown to inhibit CYP3A4. Regular orange juice, however, has no effect on the enzyme. In addition, limited data suggest that lime, star fruit, and pomegranate juice may reduce CYP3A4 activity.<sup>1,2</sup>

Several features of interactions with grapefruit juice should be considered when evaluating patients:

- Grapefruit juice interacts only with object drugs that are administered orally
- Drugs that are primarily metabolized by CYP3A4 and have a bioavailability of 50% or less are most likely to have an interaction of large magnitude with grapefruit juice
- The dose of grapefruit juice will markedly affect the magnitude of the interaction. Many studies have been done with double-strength grapefruit juice administered multiple times

daily. Single-strength juice taken once daily will result in a much smaller effect. For example, double-strength grapefruit juice administered 3 times daily will increase lovastatin concentrations more than 10-fold, whereas single-strength grapefruit juice taken once daily results in a 2-fold increase. Eating grapefruit pulp also will inhibit CYP3A4. Unless the grapefruit diet comes back into vogue, however, most patients will not consume enough grapefruit to cause significant interactions.

- Different grapefruit juices will have different concentrations of inhibitors and produce a different degree of inhibition of the object drug. These variations will be based on the source of the juice and even on different lots from the same source.
- The magnitude of interactions with grapefruit juice will vary 5- to 6-fold between patients
- Grapefruit juice inhibition of CYP3A4 may last for up to 24 hours after a single dose and up to 72 hours after multiple daily dosing

Grapefruit juice also has been shown to reduce the plasma concentration of several drugs. The absorption of fexofenadine and the beta-blockers celiprolol and talinolol is reduced by grapefruit juice.<sup>3</sup> Neither fexofenadine nor celiprolol is metabolized. The reduction in their plasma concentrations appears to be caused by grapefruit juice inhibiting the organic anion–transporting polypeptide (OATP), which assists in the uptake of drug molecules from the intestinal lumen into the enterocyte. The inhibition of OATP by grapefruit juice would reduce the absorption of drugs transported by this transporter. Orange juice has been demonstrated to produce similar effects on fexofena-



dine and celiprolol. More recently, orange juice administration reduced atenolol AUC by 40% without changing its half-life.<sup>4</sup> Apple juice also reduced fexofenadine AUC and appears to be an inhibitor of OATP.

The OATP family of proteins has been identified as transporters for a number of drugs including fexofenadine, thyroxine, pravastatin, methotrexate, digoxin, penicillin, zidovudine, and acyclovir.<sup>5</sup> These transporters have been identified in the intestine, liver, kidney, and brain. The action of OATP can be complex. For example, in the kidney, OATP may assist the transport of drugs from the blood into the urine or the reabsorption of drug back into the blood.

Thus, the inhibition or induction of these transporters can alter the usual uptake (from the intestine), reuptake (from the kidney), or elimination (from the liver or kidney) of drug molecules. The elucidation of substrates and inhibitors of these transporters will enable the identification of drug interactions that may be of clinical significance. <sup>PT</sup>

*For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Stahl, Pharmacy Times, 241 Forsgate Drive, Jamesburg, NJ 08831; or send an e-mail request to: [astahl@ascendmedia.com](mailto:astahl@ascendmedia.com).*



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