

Drug Interactions with Fruit Juices

Fruit juices can significantly alter the pharmacokinetics of drugs. Oral availability may increase or decrease depending on the type of juice consumed and whether the drug is a substrate for specific enzymes and transporters in the intestinal wall. This bulletin describes the mechanism for these interactions and summarises the fruit juices and drugs involved.

Drug interactions with grapefruit juice are some of the most clinically important and well documented. Since the first published report in 1991, over 30 drugs have been found to interact with grapefruit juice. Two varieties of oranges can also interact with drugs. Seville (or 'sour') oranges are used primarily for making marmalade and as a herbal remedy (bitter orange). Table-variety 'sweet' oranges are usually consumed raw or made into juice. Both can cause drug interactions, although the mechanisms and drugs involved appear to be different. Other fruits and their juices including apple, lime, lemon, pomelo and tangerine also appear to have drug interaction potential.¹

Mechanisms in the intestinal wall (Figure 1):

1. Inhibition of CYP3A4

The cytochrome P-450 enzyme CYP3A4 is found in the epithelial cells of the small intestine (enterocytes) as well as the liver and elsewhere. Drugs that are substrates for CYP3A4 are partially metabolised as they cross the gut wall. Grapefruit, Seville orange and lime juices inhibit intestinal CYP3A4² and increase the oral availability of several drugs¹ (see Table 1).

2. Inhibition of P-glycoprotein

P-glycoprotein (P-gp) is a transporter that protects the body from toxins and drugs by actively pumping these out of the enterocyte into the intestinal lumen. Both grapefruit juice and sweet orange juice inhibit intestinal P-gp *in vitro*.^{3,4} However, P-gp is easily saturated by high drug concentrations in the intestinal lumen suggesting that it may play only a minor role in drug interactions.⁵ In addition, P-gp and CYP3A4 share many substrates, making the relative contribution of P-gp difficult to determine.

3. Inhibition of OATP

Organic Anion Transport Polypeptides (OATP) are a group of transporters found in enterocytes, hepatocytes and elsewhere. At least two subtypes in the intestinal wall, OATP2B1 and OATP1A2, assist in the uptake of some drugs. Grapefruit, sweet orange and apple juices inhibit intestinal OATP and decrease the oral availability of the OATP substrate fexofenadine.

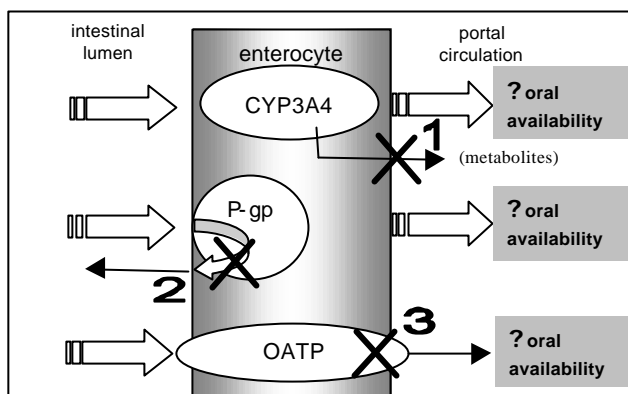


Figure 1. Fruit juice-drug interactions in the intestinal wall.
1 - inhibition of CYP3A4. 2 - inhibition of P-glycoprotein (P-gp). 3 - inhibition of OATP.

Interactions causing - oral availability (Table 1)

Grapefruit juice can dramatically increase the oral availability of several drugs. Those affected:

- ♦ are substrates of CYP3A4 and P-gp, and
- ♦ have low intrinsic oral availability, resulting from substantial pre-systemic (first-pass) metabolism.

Since inhibition of intestinal CYP3A4 can last up to 24 hours, patients on interacting medicines should avoid grapefruit and grapefruit juice entirely.

Seville orange juice can also inhibit intestinal CYP3A4 and could, theoretically, interact with the same range of drugs as grapefruit. Increased oral availability of felodipine and dextromethorphan has been demonstrated using undiluted Seville orange juice. However, Seville oranges have a bitter taste and are not usually consumed in this way. Whether 'normal' sources of Seville oranges, such as marmalade and bitter orange, cause drug interactions has yet to be determined.

Table 1. Clinically important fruit juice/ drug interactions that ↑ oral availability

Amiodarone	GFJ	Midazolam	GFJ
Atorvastatin	GFJ	Nifedipine	GFJ
Buspirone	GFJ	Nimodipine	GFJ
Carbamazepine	GFJ	Saquinavir	GFJ
Ciclosporin	GFJ	Sildenafil	GFJ
Cisapride	GFJ	Simvastatin	GFJ
Erythromycin	GFJ, SOJ	Sirolimus	GFJ
Felodipine	GFJ	Tacrolimus	GFJ
Ergotamine	GFJ	Tadalafil	GFJ
Ethinylestradiol	GFJ	Triazolam	GFJ
Erythromycin	GFJ	Vardenafil	GFJ
Felodipine	GFJ, SOJ, LJ	Verapamil	GFJ

Key: GFJ – grapefruit juice, SOJ – Seville orange juice, LJ – lime juice

Interactions causing - oral availability (Table 2)

Fruit juices, including grapefruit, sweet orange and apple, can also decrease the oral availability of some drugs. These interactions are not well understood. Several mechanisms have been proposed including: gastrointestinal pH changes, and chelation with fruit juice components. Inhibition of intestinal OATP may also be an important mechanism however, to date this has only been shown for fexofenadine.

Table 2. Clinically important fruit juice/ drug interactions that ↓ oral availability

Atenolol	OJ
Celiprolol	OJ, GFJ
Etoposide	GFJ
Fexofenadine	OJ, GFJ, AP
Itraconazole	GFJ
Theophylline	GFJ

Key: GFJ – grapefruit juice, OJ – sweet orange juice, AP – apple juice

REFERENCES

1. Saito M *et al.* Drug Safety 2005; 28(8): 667-694.
2. Bailey, DG *et al.* Clin Pharm Ther 2003; 73: 529-37.
3. Di Marco MP *et al.* Life Sciences 2002; 71: 1149-1160.
4. Takanaga, H *et al.* J Pharm Exper Ther 2000; 293: 230-236.
5. Lin JH and Yamazaki M. Clin Pharmacokinetics 2003; 42: 59-98.
6. Dresser GK *et al.* Clin Pharmacol Ther 2002; 71: 11-20