

Don't take your medicine with fruit juice!

Dr Geraldine Moses
BPharm, DClinPharm, AACPA



Geraldine Moses is a doctor of clinical pharmacy, specialising in drug information. She works part-time at the Mater Hospital in Brisbane within the Academic Practice Unit and provides a national drug info service for the ADA, called Pharm-Advice. She is also an accredited pharmacist, providing HMRs in her local community and training those who wish to become accredited.

Together with Debbie Rigby, Geraldine runs seminars on managing drug interactions.

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You've probably heard about grapefruit juice (GFJ) interacting with prescription drugs. The risk is real, can occur with as little as 200ml of juice and is quite significant... drug levels can increase up to 2-3 fold.⁽¹⁾ In the past few years however, new research has shown that other juices, particularly apple and orange juice, can also significantly alter drug absorption but in the opposite way to GFJ.⁽²⁾ Serum drug levels go down.

Fruit juice drug interactions are clinically relevant for two reasons. Firstly, because the increase or decrease in drug levels can be dramatic, and secondly because the greatest impact of the interaction occurs when fruit juice is given simultaneously, and many people take their medications with a swig of fruit juice! In fact, I recently received an enquiry from a man whose wife was undergoing cancer chemotherapy and had also embarked upon a "detox" program drinking about 3 litres of freshly-squeezed fruit and vegetable juice throughout the day. He wanted to know whether this juice could interfere with her chemotherapy. As it turns out, the answer is a resounding YES.

Mechanisms

Drug interactions with GFJ are caused by furanocoumarin bioflavonoids in the fruit blocking CYP3A4 enzymes in the gut wall, thus preventing them from being metabolised as they pass through the gut wall (via enterocytes) and the liver (in hepatocytes). As a result, systemic levels of drugs subject to this metabolism can increase. HINT: Only drugs **exclusively** metabolised via CYP3A4 are likely to interact with GFJ significantly.

Orange and apple juice have a different effect. They contain bioflavonoids called hesperidin and phlorizin (and others) which can block organic anion transport protein (OAT-P), a membrane-bound transport protein in the gut wall that pumps both endogenous and exogenous compounds into enterocytes and

hepatocytes on their way to the systemic circulation.⁽³⁾ When these bioflavonoids block OAT-P, serum levels of drugs reliant on this pathway will decline.

A good example of a fruit juice-drug interaction is that which occurs between apple juice and atenolol, a commonly used antihypertensive. Atenolol is totally dependent on OAT-P 1A2 for transport across the gut wall. A recently published study found that 600 ml apple juice consumed over 1.5 hours after atenolol administration caused a 58% reduction in atenolol levels and 1200 ml apple juice consumed over 3 hours lead to an average 82% reduction in levels.⁽⁴⁾ A study involving another beta blocker called celiprolol found 200 ml orange juice administered within 2 hours reduced plasma celiprolol concentrations by an average of >80% compared with administration with water.⁽⁵⁾ The result would be that both these drugs would be rendered ineffective by the effect of these fruit juices.

Luckily OAT-P blockade only lasts for a matter of hours, so the key issue is timing. The most significant interactions occur when the juice is given within 2 hours of drug administration, and it appears the interaction can be avoided completely if they are separated by four hours or more.⁽³⁾

The OATP family of proteins has been identified as transporters of many important drugs including fexofenadine, digoxin, pravastatin, rosuvastatin, methotrexate, 5-fluorouracil, thyroxine, penicillin, zidovudine, acyclovir and many more. Note the penicillin! And these transporters have been identified not just in the intestine and liver but kidney and brain as well. So no doubt, the physical effects of fruit juice-drug interactions are very complex. In the meantime, it would be wise to advise your patients to take their medicines with water rather than fruit juice.

Drugs with significant interactions with grapefruit juice	Drugs with significant interactions with apple and orange juice
Felodipine	Fexofenadine
Estrogen	Atenolol
Simvastatin	Erythromycin
Caffeine	Digoxin
Quetiapine	Rosuvastatin
Oxycodone	Thyroxine
Zolpidem	Aliskiren

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