



Grapefruit–drug interactions

A review article details the evidence for a pharmacokinetic interaction between grapefruit and certain drugs, and the potential clinical consequences of this.

Overview: A pharmacokinetic interaction between grapefruit and certain drugs was first identified over 20 years ago. To date, more than 85 drugs have the possibility of interacting with grapefruit, many of which are widely prescribed for important or common medical conditions. The main interaction results from interference in the activity of the cytochrome P450 3A4 (CYP3A4) enzyme.

Current advice: The British National Formulary [Appendix 1 Interactions](#) lists the drugs that interact with grapefruit juice, and advises on whether concomitant use should be avoided. More specific advice is given in the relevant Summary of Product Characteristics for each drug.

The Medicines and Healthcare Regulatory Agency (MHRA) has issued specific warnings about statins and grapefruit juice in 2 editions of Drug Safety Update ([atorvastatin](#), January 2008, and [simvastatin](#), August 2012).

New evidence: A review article ([Bailey et al. 2012](#)) has stated that drugs that interact with grapefruit have all of the following characteristics: they are administered orally, they have very low to intermediate absolute bioavailability, and they are metabolised by CYP3A4. Grapefruit juice contains furanocoumarins which can cause irreversible inhibition of CYP3A4, mainly in the small intestine. This results in reduced pre-systemic metabolism of the affected drug, and increased systemic exposure. As an editorial in the BMJ points out, the clinical consequences of this interaction can vary from an asymptomatic increase in drug concentrations to potentially life-threatening events ([Pirmohamed 2013](#)).

Case reports of serious adverse events related to grapefruit-drug interactions include torsade de pointes with amiodarone and rhabdomyolysis with atorvastatin and simvastatin. Other drugs that could be affected by grapefruit include anticoagulants (apixaban, rivaroxaban), calcium channel blockers (amlodipine, felodipine, verapamil), central nervous system drugs (quetiapine, buspirone), cytotoxics (nilotinib, lapatinib), and immunosuppressants (cyclosporin, tacrolimus, sirolimus). This list is not exhaustive. Interactions are drug-specific, not a class effect, and the British National Formulary or Summary of Product Characteristics should be referred to for further information.

The review article discusses that all sources of grapefruit (the fruit itself, freshly squeezed juice or juice from concentrate) and certain related citrus fruit (Seville oranges, limes and pomelos) can inhibit CYP3A4. A single usual amount of grapefruit (200–250 ml juice or a whole fruit) has sufficient potency to cause a pharmacokinetic interaction, which can persist long enough to affect interacting drugs that are administered once daily at any time during the dosing interval. However, the effect on drug pharmacokinetics also seems to be greater with regular consumption, suggesting a cumulative inhibitory action. The review article also suggests that older people have the greatest likelihood of eating grapefruit and taking interacting medications, and are most vulnerable to the adverse clinical consequences.



Commentary: "This review provides a comprehensive background to the pharmacokinetics of grapefruit-drug interactions. Of particular importance is the table listing the drugs with the potential to interact with grapefruit – a list that is wider than one may suspect. Also of interest to practitioners is the information on the amount of grapefruit that could cause a clinically significant effect and that all forms of grapefruit have the potential to cause the interaction.

"The true extent of grapefruit-drug interactions in clinical practice is not clear, and this review is not able to provide such data. Under-reporting of such interactions via adverse drug reaction reporting to the MHRA in day-to-day clinical practice is likely and the [yellow card system](#) provides a straightforward mechanism for reporting any suspected events.



"The difficulty for clinical practitioners is how to translate the contents of the article into sensible practice. On the basis of the article, it seems sensible to advise patients taking any drug listed as having a high potential for a clinically significant drug interaction to avoid grapefruit. For those drugs where the risk is thought to be lower, the clinical practitioner will need to gather information from the patient on the amount and frequency of grapefruit consumption, check the Summary of Product Characteristics closely for advice, and then aim to provide a reasoned judgement.

In practice, many clinicians may prefer to err on the side of caution and advise all patients taking lower-risk drugs to also avoid grapefruit. Practitioners will need to refrain from giving 'avoidance advice' to all drugs within a class, even if this is easier, and to ensure that the advice is tailored to the drug concerned. There is also a need for education and increased awareness of this drug interaction among all involved in prescribing and medicines optimisation.

"When advised to avoid grapefruit, patients may ask if the advice applies to other fruit or fruit juices. In this regard the article highlights some additional citrus fruits which may interact, but does not provide substantial additional information." – **Narinder Bhalla, Consultant Pharmacist, Medication Safety, Cambridge University Hospitals NHS Foundation Trust.**

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