

# Potentially Significant Versus Clinically Significant Drug Interactions: Pomegranate Juice as a Case in Point

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Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.

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## ABSTRACT

In vitro and in vivo laboratory data show that pomegranate juice consistently inhibits intestinal CYP2C9 and CYP3A4 enzymes. Pomegranate juice may therefore increase the bioavailability of drugs that are metabolized by these enzymes. However, studies in humans find that pomegranate juice does not increase exposure to either CYP2C9 or CYP3A4 substrates. These contradictory findings suggest that potential drug interactions identified in the laboratory may not necessarily translate into clinically significant drug interactions in humans, and hence that laboratory data are insufficient grounds upon which clinical decisions may be based.

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## Clinical Problem

Ms C has been prescribed quetiapine as maintenance therapy for bipolar disorder.<sup>1</sup> She is fond of pomegranate juice, especially because she has read much about its potential health benefits.<sup>2,3</sup> Quetiapine is metabolized by CYP3A4,<sup>4</sup> and there is literature indicating that pomegranate juice inhibits this enzyme.<sup>5</sup> Should the target dose of quetiapine be lowered to compensate for CYP3A4 enzyme inhibition? Should she be advised to switch to another fruit juice? Or can the risk of an interaction between pomegranate juice and quetiapine be ignored with quetiapine dosing titrated to efficacy and tolerability?

## Health Benefits of Pomegranate Juice

Fruit juices are popular not merely because they are pleasing to the palate but because they are perceived to contain nutrients that are important to health. Pomegranate juice, for example, has been suggested to have strong anti-inflammatory, antioxidant, antiobesity, antidiabetic, and antitumoral properties.<sup>2,3</sup> Many patients may be consuming pomegranate juice with or without their doctor's knowledge. Is there a risk of drug interactions with pomegranate juice, much as there is with grapefruit juice<sup>6</sup>?

## Pomegranate Juice and Potential Drug Interactions

Grapefruit juice drug interactions are well described in literature.<sup>6</sup> A large number of in vitro and in vivo laboratory studies suggest that, like grapefruit juice, pomegranate juice inhibits intestinal CYP3A4, resulting in increased bioavailability, increased peak drug concentration, and increased overall exposure (area under the curve) of drugs that are substrates of this enzyme; drug half-life, however, is little affected, suggesting that hepatic CYP3A4 is not inhibited. The enzyme inhibition wears off only after 1–3 days, implying that ingestion of medication several hours apart from ingestion of the juice will not prevent the interaction.<sup>5</sup>

Pomegranate juice also inhibits intestinal CYP2C9.<sup>5</sup> A large number of drugs in psychiatry are substrates of CYP2C9 and CYP3A4. Quetiapine, the drug referred to in the case presented at the beginning of this article, is an example of a CYP3A4 substrate.<sup>4</sup> Therefore, pomegranate juice has the potential to increase the exposure to and the adverse effects of quetiapine. However, there is no literature, as yet, on interactions between pomegranate juice and quetiapine.

## The Clinical Significance of CYP Enzyme Inhibition by Pomegranate Juice

Three well-conducted studies in humans evaluated drug interactions associated with pomegranate juice intake. Hanley et al<sup>7</sup> found that the positive control fluconazole but not pomegranate juice or its extract inhibited CYP2C9 and increased exposure to flurbiprofen. These

- In vitro studies and animal studies show that pomegranate juice inhibits intestinal cytochrome P450 (CYP) 2C9 and CYP3A4 enzymes, resulting in increased exposure to drugs that are metabolized by these enzymes.
- Human studies show that pomegranate juice has no effect on the bioavailability or pharmacokinetics of representative CYP2C9 and CYP3A4 substrates.
- Clinicians should evaluate the risk of drug interactions based on studies conducted in humans and not on data from laboratory studies; the latter have guidance value only when human data are unavailable.

authors<sup>7</sup> concluded that the risk of a pharmacokinetic interaction is negligible if pomegranate juice is consumed by patients receiving CYP2C9 substrates.

Farkas et al<sup>8</sup> found that the once-daily ingestion of pomegranate juice did not affect the oral bioavailability and pharmacokinetics of midazolam, a CYP3A4 substrate; in contrast, the positive control grapefruit juice inhibited both intestinal and hepatic CYP3A4. In a 2-week crossover study of twice-daily pomegranate juice intake, Misaka et al<sup>9</sup> found that pomegranate juice had no effect on the peak concentration, area under the curve, or metabolism of oral midazolam.

### Weighing the Evidence

Evidence comes from different sources: in vitro studies, animal studies, and human studies. Often, in the absence of clinical data, decisions are influenced by laboratory data. In the case of pomegranate juice, the laboratory data suggest potential drug interactions involving intestinal CYP2C9 and CYP3A4. The limited clinical data available, however, suggest that these interactions may not occur in humans and are therefore unlikely to be clinically significant. Pomegranate juice may therefore be safely consumed by patients receiving drugs that are substrates of CYP2C9 and CYP3A4.<sup>5,7</sup> With regard to the case presented at the beginning of this article,

it is likely that quetiapine can be safely prescribed without concerns about a possible interaction with pomegranate juice.

### Parting Notes

1. The reviewed evidence suggests that pomegranate juice may not result in clinically significant drug interactions in humans.<sup>5,7-9</sup> However, in the absence of direct study of the pomegranate juice–quetiapine interaction, conclusions cannot be drawn with absolute certainty.

2. Preclinical data show that pomegranate juice also inhibits intestinal CYP3A2 and P-glycoprotein, besides inhibiting hepatic sulfoconjugation.<sup>5</sup> However, the clinical significance of these effects also remains to be established.

3. There are many possible explanations for the discrepant human and animal findings with regard to pomegranate juice–mediated drug interactions<sup>5</sup>; for these and other reasons, laboratory data should be considered for guidance only when human data are unavailable.

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