

Author's response to reviews

Title: Medicinal Importance of Grapefruit Juice and Its Interaction With Various Drugs

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Author's response to reviews: see over

Thank you for your comments on our manuscript.

Changes have been made in the manuscript in line with the reviewers comments (detailed as under). All changes in the manuscript have been highlighted in blue for the convenience of the editors and the reviewer.

1. Many preceding reviews have been published in this theme. The authors need to explain the aim of this article and cite preceding works such as follows as reference.

Greenblatt DJ et al. J Clin Psychopharmacol. (2001) 21:357-9.

Bailey DG et al. Am J Cardiovasc Drugs. (2004) 4:281-97.

Saito M et al. Drug Saf. (2005) 28:677-94.

Bailey DG et al. Br J Clin Pharmacol. (1998) 46: 101-10.

Fuhr U. Drug Saf. (1998) 18: 251-72.

The following sentences have been added to the last paragraph of the introduction section in an attempt to explain the aim of this article.

In recent years, more drugs have been investigated for their interaction with grapefruit juice and new models have been proposed for the mechanism of such interaction. This article presents a simplistic summary of most examples of such interactions and also explores the phytochemistry and possible mechanisms of action involved in drug-grapefruit juice interactions in light of recent studies on this subject.

Bailey DG (2004), Saito M (2005), Bailey DG (1998) and Fuhr U (1998) have been cited at various points in the manuscript as suggested. They are highlighted blue in the references section as well. Appropriate changes in the numbering of the references have also been made in the text as well as the references section.

2. The authors cited as "(GFJ) cause activation of Pgp in vitro", but recent studies shows that GFJ inhibit Pgp.

Honda Y et al. Br J Pharmacol. (2004) 143(7):856-64.

Romiti N et al. Life Sci. (2004) 76(3): 293-302.

The suggested articles have been cited and the following lines have been added to incorporate the findings of these studies:

However, recent studies have demonstrated the inhibition of Pgp by grapefruit juice both by its down-regulation and inhibition of function [26,27]. For example, grapefruit juice increases the bioavailability of cyclosporine. This effect is thought to be primarily through Pgp inhibition (instead of CYP3A4 inhibition) since orange juice mediated reduction in enterocyte CYP3A4 concentrations did not produce a similar increase in bioavailability [17]. In fact, grapefruit juice has also shown

inhibition of multidrug resistant protein 2 (MRP2), an efflux protein closely related to Pgp in terms of its expression and function [26].

3. The marked reduction of bioavailability of nonmetabolized OATP substrate such as fexofenadine via inhibition of OATP is observed, not only GFJ but also orange juice. The authors need to emphasize this effect in the text.

Dresser GK et al. Clin Pharmacol Ther. (2002) 71:11-20.

Dresser GK et al. Eur J Clin Invest. (2003) 33 Suppl 2:10-6.

The following sentences are part of the manuscript in line with the suggestions of the reviewer:

Similarly, grapefruit and even orange juice have also recently been shown to be potent in vitro inhibitors of a number of organic anion-transporting polypeptides (OATPs) that are involved in apical-to-basal transport of drugs in the small intestine [17-18][25][29]. They were also found to decrease the absorption of the non-metabolized OATP substrate, fexofenadine hence pointing towards inhibition of intestinal uptake transporters by fruit juices to decrease drug bioavailability. This newly proposed mechanism of action and its effect vis a vis various medications also demands further investigation [25][29].

4. Both cisapride and terfenadine have been globally withdrawn from the market due to the drug-drug interaction. The authors need to mention it for the convenience of readers.

The following sentence has been added on page 16 as suggested:

Incidentally, both terfenidine and cisapride have been globally withdrawn from the market due to serious cardiac arrhythmias precipitated by their interaction with other drugs if simultaneously taken.