COMMENTS

Response to Comments by Steven Dentali

ADRIANE FUGH-BERMAN AND ADAM MYERS[1]

Department of Physiology and Biophysics, Georgetown University, Washington, DC 20057

It is certainly true that extracts made from the whole fruit of Seville orange (*C. aurantium*) may have different effects than juice extracts, but both types of extracts are available. Besides, a whole-fruit extract would include rind, and some of the compounds that affect drug metabolism would be expected to be higher in rind than juice. In grapefruit, 6′,7′ dihydroxybergamottin, which is implicated in drug interactions, is most concentrated in the rind or in oil extracted from the peel, probably because furanocoumarins require light for synthesis (1). As we noted in our review, *C. aurantium* contains not only 6′,7′ dihydroxybergamottin but also bergapten. Both furanocoumarins inhibit cytochrome P450 3A4.

The clinical study referenced by Dr. Dentali was presented as a poster at the American Society for Clinical Pharmacology and Therapeutics and has been published only in abstract form. It apparently looked at the effect of several herbs, including an extract of *C. aurantium*, on probe drugs assessing cytochrome P450 3A4 and other isozymes. The abstract does not mention doses and does not contain enough information to evaluate. We look forward to seeing the full study published.

We agree with Dr. Dentali that intravenous preparations have a stronger and faster effect than oral preparations and, as we stated in our review, that *C. aurantium* extracts may have different effects than synephrine on hemodynamic parameters. We definitely need more studies on the acute effect of *C. aurantium* extracts on blood pressure in normotensive and hypertensive humans. A dearth of definitive data in this area, however, does not imply that *C. aurantium* is safe.

We assume that the herbal product manufacturers that AHPA represents believe that *C. aurantium* is effective for weight loss. While no reliable data to date support efficacy, any substance with metabolic effects leading to weight loss would be expected to affect physiological parameters, including possibly blood pressure.

[1] To whom correspondence should be addressed at 3900 Reservoir Road N.W., Washington, DC 20057. E-mail: myersa@georgetown.edu

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1. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, He K, Lown KS, Woster PM, Rahman A, Thummel KE, Fisher JM, Hollenberg PF, Watkins PB. Mechanisms of enhanced oral bioavailability of CYP3A4 substrates by grapefruit constituents. Drug Metab Dispos 25(11):1228–1233, 1997.