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File: ■ Bitter Orange (*Citrus* × *aurantium*)
■ *p*-Synephrine
■ Safety

HC 031322-475

Date: June 28, 2013

RE: Bitter Orange Is Found to be Safe in Healthy Adults after Intake for Two Months

Kaats GR, Miller H, Preuss HG, Stohs SJ. A 60 day double-blind, placebo-controlled safety study involving *Citrus aurantium* [*sic*] (bitter orange) extract. *Food Chem Toxicol*. May 2013;55:358-362.

Bitter orange (*Citrus* × *aurantium*) is a popular supplement among athletes and dieters, primarily because of its constituent *p*-synephrine, the primary protoalkaloid. The safety of *p*-synephrine has not been established, though there have been no direct adverse event reports made for it. The reason for concern is its structural similarity to ephedrine, norepinephrine, and *m*-synephrine (phenylephrine), which have been known to have detrimental cardiovascular effects in some instances. Because bitter orange extract is often consumed with other supplements, including caffeine, it is difficult to understand what role bitter orange itself may have had in adverse events reported for the combinations. Therefore, this double-blind, placebo-controlled study sought to evaluate the safety of bitter orange, alone and in combination with the citrus flavonoids naringin and hesperidin, in healthy adults.

Seventy-five healthy adults (27-76 years of age; average age = 51.6 years; 15 males and 60 females), with an average body mass index (BMI) of 30.8 kg/m^2, were randomly assigned to receive 2 doses daily for 60 days (to be taken before breakfast and between 3 p.m. and 4 p.m.) of either 49 mg of *p*-synephrine alone; 49 mg of *p*-synephrine with 576 mg of naringin and 100 mg of hesperidin; or placebo. The *p*-synephrine supplied for both treatment groups was Advantra Z® (Nutratech, Inc.; West Caldwell, New Jersey); the source of the hesperidin and naringin was not reported. Resting heart rate, blood pressure, an 84-item Quality of Life Inventory, and a fasting 44-item blood chemistry test were obtained at baseline.

Of the 75 subjects, 67 completed the study (13 males and 54 females); and attrition was equal in all groups. No adverse events were reported by the participants at the end of the study. There were no statistically significant changes from baseline in the blood chemistry, systolic or diastolic blood pressure, resting heart rate, heart, liver, kidneys, or quality of life in any of the groups. There was a small, but statistically significant,

difference in the increase of the average resting heart rate between the combination group (3 beats per minute) and the *p*-synephrine-only (0.1 beat per minute) and placebo groups ($P < 0.05$ for both). However, the differences were not considered clinically significant; the placebo group average resting heart rate unaccountably dropped 3.3 beats per minute.

This study was by far the longest safety test of bitter orange alone, with past studies being no longer than 1 day. In another study with a bitter orange extract that contained 47 mg of *p*-synephrine where heart rates rose 11.4 beats per minute after 6 hours with an acute dose, the authors argue that the increase happened at a time point too far after the half-life of *p*-synephrine (2-3 hours) to be attributed to it. In addition, other studies have shown that *p*-synephrine binds poorly to the adrenergic receptors compared to norepinephrine, ephedrine, and *m*-synephrine, which could explain a lack of potential adverse cardiovascular effects. This study indicates that a daily dose of nearly 100 mg of *p*-synephrine taken for up to 60 days is safe in healthy male and female adults. Efficacy studies need to be done to determine if there would be any effects on weight loss.

—Risa Schulman, PhD

Peer Reviewer's Comment:
A significant shortcoming of this study was that plasma levels of *p*-synephrine were not measured so as to correlate any pharmacodynamic effect(s) or the lack thereof. The combination of *p*-synephrine and caffeine is still a major concern among some health professionals and researchers, and this paper did not address this issue.

The American Botanical Council has chosen not to reprint the original article.