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File: ■ Bitter Orange (*Citrus* x *aurantium*)
■ *p*-Synephrine
■ Weight Loss

HC 101261-459

Date: October 31, 2012

RE: Review of the Safety and Efficacy of Bitter Orange Use for Weight Loss

Stohs SJ, Preuss HG, Shara M. A review of the human clinical studies involving *Citrus aurantium* [*sic*] (bitter orange) extract and its primary protoalkaloid *p*-synephrine. *Int J Med Sci*. August 29, 2012;9(7):527-538.

Bitter orange (*Citrus* x *aurantium*) peel and fruit has a variety of traditional uses, including for the treatment of insomnia, gastrointestinal problems, and as an expectorant.[1] In traditional Chinese medicine, it is known as "Chih-shih" or "Zhi shi." The extract has been found to activate metabolism and suppress the appetite; it is thus used in supplements for weight loss. The safety of bitter orange has been confounded by the confusion between the bitter orange compound *p*-synephrine and a structurally different synthetic compound, *m*-synephrine. Other conflicts surrounding the safety of bitter orange include the lack of standardization of tested material, studies including mixtures of bitter orange with other botanicals, and misinformation on adverse side effects. This review focuses on the safety and efficacy of bitter orange and *p*-synephrine gathered from published studies, case reports, and unpublished material (research reports from the Internet or investigators and meeting presentations).

An initial study tested a mixture of 975 mg of bitter orange extract standardized to 6% synephrine alkaloids, 528 mg of caffeine, and 900 mg of St. John's wort (*Hypericum perforatum*) taken daily by obese adult subjects (n=20). All subjects also participated in a standardized diet and exercise program. The groups consuming the mixture lost 1.4 kg of weight, 2.9% body fat, and had activated metabolic rates after 6 weeks; however, it is not possible to separate the contributions of the different ingredients. Adverse effects were not noted in this study.

In another unpublished study, overweight subjects given a product containing 125 mg of bitter orange extract (Advantra Z®; Nutratech, Inc.; West Caldwell, New Jersey), 125 mg of hydroxycitric acid (Citrimax™; Nature's Plus; Long Beach, California), and 50 mg of kola (*Cola nitida*) nut extract for 10 weeks lost more weight when also modifying diet and exercise (6.59 kg) than subjects consuming only the product (4.63 kg) or only modifying diet and exercise (3.45 kg; no P-values given). No adverse side effects were reported in this study.

To assess whether *p*-synephrine had any effect on the cardiovascular (CV) system, one crossover study had 12 subjects take either orange juice (standardized to contain 13 mg of *p*-synephrine) or water. Neither heart rate nor blood pressure was significantly different between groups, but the study advised against consuming the juice based on mistakenly assuming it contained *m*-synephrine.

In a series of small, double-blind, crossover studies, the product Xenadrine EFX® (Cytogenix Laboratories; New York, New York), containing 12 mg of *p*-synephrine, yerba mate (*Ilex paraguariensis*), grape (*Vitis vinifera*) seed, green tea (*Camellia sinensis*), and ginger (*Zingiber officinale*) root, in addition to several vitamins and amino acids, showed a significant stimulation of resting metabolic rates in healthy subjects (n=10) as compared to a control group. This same group also tested this product along with exercise in healthy subjects (n=16) and reported a significant decrease in fatigue along with a decrease in diastolic blood pressure in the treated group as compared to the placebo group. Subjects did not experience weight loss or any effect on multiple CV parameters; in addition, sleep problems were reported by those in the treatment group.

The same team also investigated another product (Xenadrine™; Cytogenix Laboratories), which consisted of 5 mg of *p*-synephrine, 20 mg of ephedrine, 200 mg of caffeine, and 15 mg of salicin. When combined with diet and exercise in overweight subjects, this product led to significant weight loss as compared with the control group after 8 weeks (3.14 kg vs. 2.05 kg, respectively; no P-values given).

Moreover, this group investigated the CV effects of Xenadrine RFA-1™ (Cytogenix Laboratories), containing 20 mg of ephedrine, 5 mg of *p*-synephrine, and 200 mg of caffeine in 2 capsules, in a double-blind, placebo-controlled, crossover study in 27 healthy, overweight individuals. No significant differences in heart rate, blood pressure, or heart function were detected. A subsequent commentary on this study investigating adverse side effects observed dry mouth, sleep problems, and increased activity in subjects, but there were no serious adverse side effects or impacts on CV parameters for the treatment or placebo groups.

In another study, it was reported that a bitter orange extract did not affect the activity of the liver enzyme cytochrome P450, suggesting potential safety with regards to herb-drug interactions. No adverse side effects were observed. The authors did not assess effects on weight or blood chemistry.

A study involving overweight adults investigated a combination of bitter orange, guaraná (*Paullinia cupana*), green tea, 7-oxo-dehydroepiandrosterone (DHEA), linoleic acid, and chromium picolinate. The researchers reported a significant weight loss in the treatment group as compared to the control group after 8 weeks (2.9 kg vs. 1.5 kg, respectively; no P-values given). No effects on CV parameters were reported, and there was no significant difference in adverse side effects between groups.

A randomized, double-blind, placebo-controlled study examined a product (Lean System 7®; iSatori Technologies, Inc.; Golden, Colorado) containing 6 mg of *p*-synephrine, along with other plant extracts and components, on metabolic endpoints in overweight adults. Those consuming the product had an activated resting metabolic rate as compared to the placebo group. No other effects on CV parameters were observed, and no serious adverse side effects were seen.

Another randomized, double-blind, placebo-controlled, crossover study reported no effects of a bitter orange supplement (27 mg of *p*-synephrine; Nature's Way; Lehi, Utah) on blood pressure in healthy subjects. In an additional randomized, double-blind, placebo-controlled, crossover study with both a bitter orange extract (Advantra Z; 46.9 mg of *p*-synephrine) and Xenadrine EFX, it was found that both products increased heart rate, but the authors noted that it was not clear whether the effects were from the caffeine or the other ingredients. In a separate study, a small, but clinically insignificant elevation in heart rate and blood pressure were observed in response to supplementation with a bitter orange extract (54 mg of *p*-synephrine; Nature's Way).

In a study on metabolism, overweight subjects supplemented with Xenadrine EFX were found to have greater carbohydrate oxidation, plasma fatty acid concentrations, and elevated fatty acid oxidation to adenosine-5'-triphosphate (ATP). Another study found that a bitter orange extract elevated the thermic effect of food when combined with a protein meal. When an "enriched coffee product" (including coffee [*Coffea arabica*], 21.6 mg of *p*-synephrine, bitter orange extract, *Garcinia cambogia*, caffeine, and chromium polynicotinate; JavaFit®; Javalution Coffee Company; Fort Lauderdale, Florida) was tested in healthy subjects, resting metabolic rate and respiratory exchange ratio were elevated significantly. Systolic blood pressure also slightly increased, likely due to the caffeine content.

In an unpublished study using Advantra Z (80 mg per day of *p*-synephrine), heart rate, body weight, and blood pressure did not differ significantly between the treatment and placebo groups. This study is considered notable due to the high dosage of *p*-synephrine used. A separate study utilizing an exercise product (Ripped Fuel® Extreme Cut; Twinlab Corporation; New York, New York) containing 21 mg of *p*-synephrine along with other plant extracts found that consumption of the product prior to exercise led to elevated blood pressure and blood glucose concentrations, as well as the perception of less physical work.

In "mildly obese" subjects, an herbal blend containing Advantra Z (13 mg of *p*-synephrine), guaraná, and green tea was shown to activate calorie expenditure and oxygen uptake. Another study showed that Advantra Z (50 mg of *p*-synephrine) elevated resting metabolic rate in treated subjects as compared to control subjects. An unpublished, randomized, placebo-controlled, double-blind, crossover study evaluating the safety of *p*-synephrine supplemented healthy subjects with 49 mg of *p*-synephrine (Advantra Z) and found no effect of the compound on heart rate, blood pressure, blood cell count or general blood profile; *p*-synephrine did not negatively impact the CV system.

To assess adverse side effects potentially associated with bitter orange extract, this review considered 22 Food and Drug Administration adverse event reports. All reports described material that had multiple botanical ingredients, as well as various compounds. Adverse side effects reported ranged from heart problems, gastrointestinal conditions, and CV disorders. Other health concerns potentially confounding any results included preexisting heart problems, smoking, or high caffeine or alcohol consumption, among many others. In addition to these variables, the authors also point out that orange juice contains *p*-synephrine and is not associated with adverse side effects; this suggests that the adverse side effects reported are not sufficiently correlated with either bitter orange or *p*-synephrine.

Although the research described herein reveals that further work is necessary to determine the efficacy of bitter orange use in weight control and metabolic health, too many products used in these studies contained other compounds or plant materials with known bioactivity, such as caffeine. This can confound any observed effects on metabolism. Also, many of the studies reviewed failed to mention any adverse effects, and some are not well detailed. Despite this, most studies consistently did not detect any negative (or otherwise) effects of bitter orange or *p*-synephrine on heart rate or blood pressure, and the review of adverse event reports illuminates a lack of clear correlation between bitter orange and the reported adverse side effects. Rigorous clinical trials are warranted for possible use of bitter orange for metabolic health, especially in combination with diet and exercise.

—Amy C. Keller, PhD

Reference

[1]Stohs SJ, Preuss HG. The safety of bitter orange (*Citrus aurantium*) [*sic*] and *p*-synephrine. *HerbalGram*. 2010;(89):34-39.

Referenced article can be found at http://www.medsci.org/v09p0527.pdf.