Research Paper

Effect of Acute Administration of an Herbal Preparation on Blood Pressure and Heart Rate in Humans

John G. Seifert[1]✉, Aaron Nelson[2], Julia Devonish[2], Edmund R. Burke[3], and Sidney J. Stohs[4]

1. Movement Science/Human Performance Laboratory, Montana State University, Bozeman, MT, USA
2. Human Performance Laboratory, St. Cloud State University, St. Cloud, MN, USA
3. Dept of Biology, Colorado University – Colorado Springs, Colorado Springs, CO, USA
4. School of Pharmacy and Health Professions, Creighton University Medical Center, Omaha, NE, USA

✉ Corresponding author: john.seifert@montana.edu, 406-994-7154

Abstract

Confusion and controversy exist regarding the cardiovascular effects of dietary supplements containing caffeine and *Citrus aurantium* (bitter orange) extract. The primary protoalkaloidal ingredient in bitter orange extract is *p*-synephrine which has some structural similarities to ephedrine and nor-epinehrine, but exhibits markedly different pharmacokinetic and receptor binding properties. The goal of this study was to investigate the cardiovascular effects of a product containing caffeine, bitter orange extract (*p*-synephrine) and green tea extract in mildly overweight individuals. Fourteen female and nine male subjects (age 24.7 $\pm$7.4 yrs, BMI: 26.6 $\pm$3.8) volunteered in this randomized, placebo-controlled, crossover, double-blind designed study. On day one, subjects entered the laboratory following an overnight fast. Heart rate and blood pressure were recorded at 60 min. Expired air was analyzed for the next 10 min of the session. At each of three meals, subjects ingested one capsule that was either a non-caloric placebo or a dietary supplement that contained 13 mg p-synephrine and 176 mg caffeine. On the following day, the subjects returned and repeated the protocol for data collection beginning 60 min after consuming one capsule of the placebo or the dietary supplement. No effects of the dietary supplement on heart rate, systolic and diastolic blood pressure or mean arterial pressure were observed. No between or within group differences were observed when data were analyzed for gender and caffeine usage. A small but significant decrease in resting respiratory exchange ratio was observed for the low caffeine user group in response to the product containing caffeine and *p*-synephrine. The results of this study indicate that ingestion of a product containing bitter orange extract, caffeine and green tea extract does not lead to increased cardiovascular stress and that fat oxidation may increase in certain populations.

Key words: *Citrus aurantium*, *p*-synephrine, blood pressure, heart rate, bitter orange, caffeine, green tea

Introduction

Approximately two-thirds of the adult American population are overweight while about one-third is by definition considered to be obese [1]. The increase in obesity is associated with increased incidences of di-abetes, hypertension, hyperlipidemias, cardiovascular diseases, stroke, and premature deaths at a cost of billions of dollars annually [2, 3]. As a consequence, great emphasis is being placed on various approaches

to weight loss and weight management, including dietary supplements, diets, and exercise programs.

Citrus aurantium (bitter orange) extract and its primary protoalkaloidal constituent *p*-synephrine are widely used in weight loss and weight management products in combination with caffeine, polyphenolics, and other constituents [4-7]. These products are designed to promote thermogenesis and increase metabolism, suppress appetite, and/or slow the absorption of fats and carbohydrates [5].

In spite of their widespread use and the lack of credible reports regarding adverse effects, controversy has existed regarding the safety of bitter orange extract and *p*-synephrine [8-11]. The safety of *p*-synephrine is clouded by its structural similarity to nor-epinephrine in spite of the fact that the pharmacokinetics of the two compounds and the receptor binding specificities are vastly different due to significant structural differences [5, 12]. Furthermore, there is a lack of understanding [8, 10] between the pharmacological properties of *p*-synephrine (hydroxyl group on the para position of the benzene ring) which is found in *C. aurantium,* and *m*-synephrine (phenylephrine; with the hydroxyl group on the *meta* position) which is used in nasal decongestants and is not a constituent of *C. aurantium.*

Because of the known cardiovascular effects of nor-epinephrine and ephedrine, it has generally been assumed that consumption of *p*-synephrine and bitter orange extract will likewise result in increases in heart rate and blood pressure [8-11]. The purpose of this study was to determine the effects of the acute administration of a product containing caffeine from guarana, *p*-synephrine from *C. aurantium* and a green tea polyphenolic extract on heart rate and blood pressure in mildly overweight human subjects.

Methods

Twenty-three subjects volunteered to participate in this double blind, placebo controlled cross-over study. Fourteen subjects were female and nine were male. Table 1 summarizes the characteristics of these subjects. The Institutional Review Board approved this study prior to data collection. All subjects completed a health history questionnaire and provided informed consent prior to participation.

An uninvolved individual randomly divided subjects into two groups, 12 and 11 subjects per group. The subjects received either the experimental product in capsule form or a non-caloric placebo in a cross-over design. Following data collection, a one week washout period was provided between the two experimental procedures. Each capsule of the experimental treatment product (Acceleron®) contained *C.*

aurantium extract (AdvantraZ®, 6% *p*-synephrine yielding 13 mg *p*-synephrine), 176 mg caffeine in the form of guarana extract, and 55.5 mg of green tea extract with small amounts of other ingredients (see Table 2). While on the experimental treatment, each subject consumed four capsules for a total of 52 mg *p*-synephrine and 704 mg caffeine over a 24 hour period.

Table 1. Subject characteristics

	Age (yrs)	Height (m)	Weight (kg)	BMI
Overall	24.5 ± 7.4	1.74 ± 0.09	81.1 ± 17.1	26.6 ± 3.8
Females (n=14)	25.4 ± 9.3	1.68 ± 0.07	72.4 ± 11.8	25.5 ± 3.2
Males (n=9)	23.1 ± 2.5	1.82 ± 0.06	94.5 ± 15.7	28.3 ± 4.1

BMI: Body mass index. Each value is the mean ± SD.

Table 2. Dietary supplement ingredients per capsule

Ingredient	Amount
Guarana (caffeine)	176 mg
Citrus aurantium (*p*-synephrine)	13 mg
Green Tea Powder Extract	55.5 mg
Bee Pollen	1 mg
White Willow Bark Powder	1 mg
Panax ginseng Root	2 mg
Garcinia cambogia extract	2 mg
Vanadium	0.15 mcg

On a given treatment, day one was used to collect baseline data. All subjects were instructed to refrain from exercise 24 hours before their trial. Dietary intake was not controlled, but subjects were instructed to maintain a consistent intake from trial to trial. Subjects entered the laboratory on the scheduled morning following an overnight (12 hour) fast. They sat quietly for 30 min in a comfortable chair in a room with dim light.

Expired air was collected for 10 min from 20 to 30 min of this session as subjects breathed through a one-way breathing valve. Expired air was collected in Douglas bags and contents measured by Ametek Oxygen and Carbon Dioxide Analyzers (Thermox, Pittsburgh, PA) while volume was measured using a Tissot spirometer. Indirect calorimetry was used to determine oxygen uptake (VO_2) and carbon dioxide production (VCO_2). The non-protein respiratory exchange ratio (RER) value was calculated from VO_2 and VCO_2. The RER was used as an index of fat and carbohydrate oxidation. Heart rate (Polar HR Moni-

tor, Stamford, CT) and blood pressure (ausculatory method) were collected at 30 min.

Following baseline data collection, subjects were given three treatment capsules and instructed to ingest one capsule with each meal during that day. Subjects returned to the laboratory on the following morning after an overnight fast and were given the fourth treatment capsule with water. Subjects then sat quietly for 60 min. The 60 min period was estimated to give maximal blood levels of the ingredients [11, 13]. Expired air was then collected and analyzed during the next 10 min of the session. Heart rate and blood pressure were recorded at the end of expired air collection, approximately 72-75 min after capsule ingestion.

Three analyses of the data were performed using 2 x 2 analysis of variance (ANOVA). For the first data analysis, treatment and time were the independent factors using all 23 subjects. The second analysis separated and analyzed the data according to gender. The third analysis assessed the data for differences in high caffeine and low-caffeine users. Fourteen subjects were classified as low caffeine users and nine as high caffeine users, employing the breakpoint of 150 mg caffeine per day to separate the two groups. Statistical significance was established at $p<0.05$. All data are reported as mean $\pm$ standard deviation (SD).

Results

All 23 subjects completed the study. Based on self-report and questionnaire, all subjects ingested the given capsules on time as noted in the Methods section. No adverse treatment effects were observed or reported by any of the subjects.

Table 3 contains the cardiovascular data from the entire subject population. No statistical differences were observed within groups or between groups for any of the measures. Heart rate, blood pressure, and metabolic variables were maintained from baseline to the post-ingestion collection period regardless of treatment. Three subjects (one male and two females) were pre-existing hypertensives (systolic blood pressure > 140 mm Hg). Blood pressures for the hypertensive individuals did not change significantly in response to the dietary supplement.

Table 4 contains data separated by gender. No significant differences were observed for the dependent variables in the female group. Likewise, males did not demonstrate significant differences when the dietary supplement was ingested.

Data separated into high and low caffeine users are presented in Table 5. As with the previous analyses, no significant differences were observed for heart rates or blood pressures between the experimental and placebo control groups. However, there was a small but significant change in RER data for the low caffeine users relative to both the placebo control group and the pre-treatment baseline for the low caffeine group. After ingestion of dietary supplement the low caffeine users exhibited a decrease in RER from 0.84 ± 0.05 to 0.81 ± 0.04.

Effect sizes were calculated for each of the analyses where data were separated by gender (Table 4) or caffeine consumption (Table 5). The effects based on number of subjects per group were all below 0.4, indicating low to moderate influence.

Table 3. The effects of supplementation on cardiovascular and metabolic parameters (n=23)

Treatment	Heart Rate (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	MAP (mm Hg)	RER
PL pre	62.4 ±11.8	119.9 ±12.0	77.7 ± 8.9	91.8 ± 9.1	0.85 ±0.07
PL post	60.7 ±12.5	118.7 ±10.2	76.7 ± 7.8	90.7 ± 8.5	0.86 ±0.05
DS pre	63.5 ±14.2	119.2 ±14.3	76.9 ± 8.4	91.0 ± 9.8	0.85 ±0.06
DS post	60.9 ±12.4	118.9 ±11.1	79.2 ± 6.4	92.4 ± 7.3	0.83 ±0.07

PL: Placebo; DS: Dietary Supplement; BP: Blood Pressure; MAP: Mean Arterial Pressure; RER: Respiratory Exchange Ratio. Each value is the mean $\pm$SD.

Table 4. The effect of gender and supplementation on cardiovascular and metabolic parameters

Treatment	Heart Rate (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	MAP (mm Hg)	RER
A. Females (n=14)					
PL pre	65.9 ±13.2	117.9 ±12.6	76.3 ±10.5	90.1 ±10.4	0.86 ±0.08
PL post	65.1 ±13.1	117.2 ±12.6	76.1 ±8.9	89.8 ±9.5	0.85 ±0.05
DS pre	70.2 ±13.8	112.8 ±12.4	74.2 ±8.8	87.1 ±9.4	0.84 ±0.05
DS post	65.5 ±12.4	116.2 ±10.3	79.4 ±5.9	91.7 ±7.0	0.82 ±0.09
B. Males (n=9)					
PL pre	56.9 ±6.3	123.0 ±11.0	80.0 ±5.2	94.3 ±6.4	0.85 ±0.05
PL post	53.9 ±8.0	120.9 ±11.9	77.7 ±6.3	92.1 ±7.2	0.86 ±0.05
DS pre	53.1 ±7.0	128.1 ±11.4	91.0 ±6.2	97.1 ±7.3	0.85 ±0.06
DS post	53.8 ±8.8	123.0 ±11.6	78.8 ±7.5	93.5 ±8.0	0.83 ±0.05

PL: Placebo; DS: Dietary Supplement; BP: Blood Pressure; MAP: Mean Arterial Pressure; RER: Respiratory Exchange Ratio. Each value is the mean $\pm$ SD.

Table 5. The effects of caffeine use and supplementation on physiological responses.

Treatment	Heart Rate (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	MAP (mm Hg)	RER
A. Low Caffeine Users (n=14)					
PL pre	63.4 ±11.9	120.6±12.1	79.8 ±9.6	93.4 ±9.7	0.84 ±0.06
PL post	63.4 ±13.1	117.9±12.7	78.1 ±8.2	91.3 ±8.9	0.84 ±0.04
DS pre	65.8 (15.2	119.4±13.6	77.9 ±9.2	91.8 ±10.3	0.84 ±0.05
DS post	64.7 (13.7	120.6±11.1	80.6 ±6.3	94.0 ±7.3	0.81 ±0.04*
B. High Caffeine Users (n=9)					
PL pre	60.9 ±12.1	118.8 ±12.5	74.6 ±7.0	89.3 ±8.1	0.87 ±0.09
PL post	56.7 ±10.9	119.8 ±12.2	74.7 ±7.2	89.7 ±8.3	0.88 ±0.06
DS pre	60.0 ±12.6	118.9 ±16.2	75.2 ±7.2	89.8 ±9.5	0.86 ±0.06
DS post	55.0 ±7.3	116.1 ±11.1	76.9 ±6.2	90.0 ±7.0	0.86 ±0.10

*Significantly different from pre-ingestion value and placebo groups (P<0.05).

PL: Placebo; DS: Dietary Supplement; Heart Rate; BP: Blood Pressure; MAP: Mean Arterial Pressure; RER: Respiratory Exchange Ratio. Each value is the mean ±SD.

Discussion

The results of this study indicate that acute ingestion of a dietary supplement containing caffeine, bitter orange extract (*p*-synephrine) and green tea extract did not lead to significant cardiovascular effects as reflected by blood pressure and heart rate, regardless of treatment or subject grouping either by gender or caffeine usage. Subjects in the present study ingested 39 mg of *p*-synephrine and 528 mg of caffeine the day before testing followed by ingestion of an additional 13 mg *p*-synephrine and 176 mg caffeine the next morning after an overnight fast. This protocol more closely represents typical ingestion regimes of dietary supplements used for weight loss and weight management, and is unique as compared to other studies that involve only a single dose [11, 13-15].

Controversy exists regarding the cardiovascular effects of *C. aurantium* extract in combination with caffeine, and various authors make the assumption that an increase in heart rate and blood pressure are to be expected [8, 10, 16-19]. However, a number of studies that have assessed the cardiovascular effects of products composed of *C. aurantium* extract in com-

bination with caffeine and other ingredients have not observed an increase in blood pressure [6, 7, 11, 19-21] or heart rate [6, 7, 19-21]. The results of the present study clearly agree with these previous observations.

Haller et al. [11] examined the cardiovascular effects associated with a single dose of a multi-component dietary supplement (Xenadrine®) in 10 subjects. The supplement contained 5.5 mg *p*-synephrine, 239 mg caffeine, 5.7 mg octopamine and undisclosed amounts of other ingredients including catechin polyphenols. The hemodynamic effects of a single dose of a C. aurantium extract (Advantra Z®) that contained 46.9 mg *p*-synephrine were also examined. The results demonstrated that the dietary supplement, but not the *p*-synephrine-containing bitter orange extract, increased both systolic and diastolic blood pressures at two hours post treatment relative to the control group. No significant effects of either treatment on heart rate were noted over the first three hours after ingestion of the products. However, a significant increase in heart rate over control was noted at the six hour time point.

This study of Haller et al. [11] is complicated by the fact that all subjects consumed a meal three hours after treatment ingestion. After eating, an increase in heart rate occurred in all three treatment groups. The increase in heart rate does not coincide with the pharmacokinetics including blood levels and half–life of *p*-synephrine [11, 13], but does coincide with the thermic effect of food in this study. Given that the control group responded similarly to the two treatment groups after the meal at the four and eight hour measurements (one and five hours after the meal), the reason for the apparently significant difference seen at only the six hour time point (three hours after the meal) is unclear. No explanation is given by the authors for this change in heart rate. Gougeon et al. [19] reported that the thermic effect of food increased by 29% in 17 females after they ingested 26 mg *p*-synephrine. The thermic effect of *p*-synephrine was greater in males than females in the absence of a meal, and no significant changes occurred in pulse rates or blood pressures when compared with baseline values.

Haller et al. [13] have also examined the effects, under resting and exercise conditions, of a dietary supplement designed to enhance athletic performance in 10 subjects. The product (Ripped Fuel Extreme Cut®) contained 21 mg *p*-synephrine, 304 mg caffeine, as well as extracts of green tea, ginger root, cocoa seed, willow bark and wasabi. The placebo or product was taken one hour before 30 min of moderately intense exercise. There were no treatment- related differences in post-exercise heart rate, systolic blood pressure or body temperature. A significant prod-

uct-related increase in diastolic blood pressure (8.7 mm Hg) was observed, apparently counteracting the vasodilatory effects of exercise. Due to the poly-herbal, poly-alkaloidal and poly-protoalkaloidal nature of this product, the ingredient or ingredients responsible for the observed effect cannot be determined.

Bui et al. [15] conducted a study on 15 healthy subjects given a single oral dose of 900 mg bitter orange extract (Nature's Way) that contained 6 % *p*-synephrine (54 mg *p*-synephrine) or the placebo. Small but significant increases were observed in heart rate, and systolic and diastolic blood pressures for up to five hours. Of interest is the fact that Min et al. [18] used this same product in a similarly designed study and saw no effect in 18 subjects on systolic or diastolic blood pressure, or on the rate-corrected QT (QTc) interval.

The confusion regarding the purported cardiovascular effects of *C. aurantium* has been due, at least in part, to a lack of understanding of the differences in the pharmacokinetic and pharmacological properties between *p*-synephrine and *m*-synephrine (phenylephrine). Failure to differentiate the effects of the two isomers has resulted in a number of authors attributing the effects of *m*-synephrine to *p*-synephrine [see for example 8, 10, 17, 18, 21]. *p*-Synephrine (hydroxyl group in the para position on the benzene ring) is the isomeric form found in *C. aurantium* (bitter orange). *m*-Synephrine (hydroxyl group in the meta position) is not a constituent of bitter orange nor is it present in standardized *C. aurantium* reference materials [22]. The *m*-synephrine (phenylephrine) is readily available as an over-the-counter nasal decongestant, is also used as an ophthalmic product for mydriasis, and is known for its cardiovascular effects [23].

The differences in pharmacological properties of the *m*- and *p*- isomers of synephrine can be explained on the basis of adrenergic receptor binding. It is well known that, in general, binding to α-adrenergic receptors results in vasoconstriction, with increased cardiovascular contractility and increased heart rate occurring in response to β1-adrenergic receptor binding, while bronchodilation occurs in response to β2-adrenergic receptor binding [24]. Activation of β3-adrenoreceptors is believed to be associated with lipolysis and thermogenesis, and not adverse cardiovascular effects [25]. The belief that *p*-synephrine exerts its effects by binding primarily to this receptor is supported by experimental [26] and receptor binding studies [27].

The cardiovascular effects of caffeine are known to depend on the extent of regular exposure [28, 29]. Caffeine–naïve subjects can experience an increase in blood pressure and heart rate, while regular users of caffeine-containing products develop a tolerance to these effects. In this study, even the low caffeine users did not demonstrate an increase in these cardiovascular effects. The observation that the low caffeine intake group showed a reduction in RER may be a reflection of caffeine sensitivity. Caffeine is known to increase fat oxidation (lower RER), and this group may have been more responsive to the caffeine in the product.

Although the number of subjects used in this study is not large (n=23), this number exceeds the number of subjects used in frequently referenced studies involving bitter orange extract. For example, Haller et al. [11, 13] used 10 subjects in each study, while Sale et al.[20] used 20 subjects, Bui et al. [15] used 15 subjects and Min et al. [14] used 18 subjects. Furthermore, as noted in the results, because of the small numbers of subjects when the data were separated based on gender and caffeine intake, size effects were calculated for each of these analyses. The effects of size were low (0.2) for gender and moderate (0.4) for the low caffeine users with respect to RER.

In summary, the results of this study indicate that ingestion of a product containing bitter orange extract (*p*-synephrine), caffeine and green tea extract in a short-term dosing schedule similar to that commonly used with dietary supplements did not result in alterations in heart rate or blood pressure. However, longer term studies are required to assess these effects under conditions similar to those encountered when using the product in conjunction with a long term weight loss program.

Acknowledgements

Conflict of Interest

The authors have declared that no conflict of interest exists.

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