

## PAPER

# An acute clinical trial evaluating the cardiovascular effects of an herbal ephedra–caffeine weight loss product in healthy overweight adults

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**Objective:** This study was undertaken to determine the acute effects of a commercial weight loss supplement containing herbal ephedrine and caffeine on cardiovascular function in healthy overweight adults.

**Design:** Randomized double blind clinical trial evaluating the cardiovascular effects of an ephedra–caffeine (Xenadrine™; XEN) based herbal product vs placebo (PLA).

**Subjects:** Twenty-seven healthy overweight adults (age 21–60y; body mass index  $\geq 25$  kg/m<sup>2</sup>).

**Measurements:** Systolic and diastolic blood pressure, heart rate, serial electrocardiograms (EKG) and Doppler echocardiograms.

**Results:** A comparison of means between the groups indicated no statistically significant differences at the start of the study for the variables above. There were no serious adverse events. When examining the effects of XEN vs PLA on cardiovascular health/function, there were no significant effects observed in heart rate, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, heart valve function or in cardiovascular physiology within the parameters measured.

**Conclusion:** These findings indicate that, over a 14-day period, ingestion of the commercial weight loss supplement in a healthy overweight population did not produce any noticeable cardiovascular side effects.

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**Keywords:** caffeine; cardiovascular; ephedrine; sympathomimetic; weight loss

## Introduction

Following the passage of the Dietary Supplement Health and Education Act of 1994 a plethora of herbal products have entered the marketplace. Of concern is unrestricted or unsupervised sale of ephedrine and caffeine in herbal form. Reports of serious adverse events associated with the use of herbal ephedrine and caffeine have been reported and reviewed.<sup>1</sup> Since approximately 33% of the population is now classified as obese and 55% of the United States population classified as overweight, weight management strategies are indicated.<sup>2,3</sup> Conventional treatment of the overweight/obese includes dietary restriction, behavior modification and exercise. The overweight/obese are at increased risk for type 2 diabetes mellitus, insulin resistance, hypertension,

coronary artery disease, hyperlipidemia, stroke, endometrial, post-menopausal breast cancer, colon cancer, sleep apnea, gallbladder disease, gastroesophageal reflux disease, non-alcoholic hepatic steatosis, gout, infertility and thromboembolism.<sup>2</sup> Traditional care of the overweight/obese includes dietary counseling and restriction, behavior modification and exercise. However, this multidisciplinary approach has not worked for many patients, thus there is a recognized need for safe and effective adjunctive pharmacotherapeutic agents.

Herbal ephedrine and caffeine fall within the sympathomimetic class of pharmacotherapeutics and thus are a concern when a person at risk for undesirable side effects uses them indiscriminately.<sup>4</sup> Ephedrine can raise arterial blood pressure by causing peripheral vasoconstriction and cardiac stimulation.<sup>5</sup> The efficacy of ephedrine and caffeine for weight loss is well known, however the relative safety profile has been questioned.<sup>1,6</sup> Caffeine is often combined with ephedrine because as a methylxanthine it potentiates ephedrine's thermogenic effect (inhibits phosphodiesterase

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activity).<sup>7</sup> However, herbal ephedrine and caffeine may not have the same thermogenic potency as their synthetic counterparts. The herbal form includes five ephedra alkaloids, thereby limiting the total amount of ephedrine (contains some of the less active isomers) as compared to the synthetic ephedrine (the most active isomer). Thus the cardiotoxicity of herbal ephedrine and caffeine has not been well defined.

The aim of the present study was to compare the acute cardiovascular effects of an herbal ephedrine-caffeine containing commercial weight loss product (Xenadrine™, Cytodyne Technologies, Lakewood, NJ, USA) vs a placebo on cardiovascular health as measured by heart rate, blood pressure, serial electrocardiograms and Doppler echocardiograms.

## Research methods and procedures

### Patients and methods

A total of 30 healthy overweight/obese volunteers (19 female, 11 male) ages 21–60y were recruited for this single-center randomized double-blind placebo-controlled clinical trial. Subjects were eligible if they had a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>. Baseline characteristics include (mean): weight—Xenadrine™ group (XEN), 89.2 kg, placebo group (PLA), 82.5 kg; age—XEN, 39.35 y old, PLA, 37.4 y old; height—XEN, 167.1 cm, PLA, 166.6 cm; BMI—XEN, 31.9 kg/m<sup>2</sup>, PLA, 31.39 kg/m<sup>2</sup>; percentage body fat—XEN, 26.7%, PLA, 27.0%. There were no differences between the two groups at baseline in any of the parameters tested ( $P < 0.05$ ). Baseline data were analyzed via *t*-tests and analysis of variance (ANOVA).

Subjects were excluded if they had any personal history of heart disease, high blood pressure, renal or hepatic impairment/disease, type 1 or 2 diabetes mellitus, elevated fasting glucose ( $> 126$  mg/dl), psychiatric disorders, cancer, benign prostatic hypertrophy, used any monoamine oxidase inhibitor medication, unstable thyroid disease, were pregnant or lactating, experienced caffeine sensitivity or any medical condition deemed exclusionary by the medical staff. Furthermore, they were excluded if there had been a weight loss greater than 5 kg in the past month, they had used any prescription or commercial weight loss agent in the past month or they were allergic to any of the ingredients in Xenadrine™.

The commercial product tested chiefly contains 335 mg Ma Huang standardized for 20 mg ephedrine alkaloids, 910 mg guarana standardized for 200 mg caffeine and 85 mg bitter orange standardized for 5 mg synephrine per two capsules (one serving).

Screening included a physical, electrocardiogram (EKG), Doppler echocardiogram (Echo), systolic and diastolic blood pressure, heart rate, fasting glucose, urinary pregnancy screen, temperature and a Visual Analog Scale for sleep quality (VAS-SQ; 10 cm scale). After passing the screen, subjects entered the study. In a randomized manner subjects were either assigned to the experimental group (XEN) or the

placebo (PLA). Each subject was instructed for the first 7 days to ingest one capsule twice a day (Xenadrine™ RFA-1, Cytodyne Technologies, Lakewood, NJ, USA). For the second 7 days, each subject was instructed to ingest two capsules twice per day. Capsular ingestion was prior to breakfast and mid-afternoon (3 pm). All subjects were also asked to refrain from ingesting more than three cups of coffee daily or the caffeine equivalent. Subjects were allowed to consume their normal diet and to continue on their respective exercise routines. No additional dietary supplements or vitamins were allowed throughout the study period.

On days 7 and 14, subjects underwent repeat testing. Therefore, subjects were in the laboratory at baseline and days 7 and 14. Visits on days 7 and 14 were post-morning dose ingestion. A local laboratory (Quest Diagnostics, Miramar, FL, USA) processed all blood work. Tests conducted on days 0, 7 and 14 included EKG (Burdick Eclipse 800, Deerfield, WI, USA), systolic and diastolic blood pressure, heart rate, temperature and VAS-SQ. In addition, on day 14 all subjects also underwent a repeat Doppler echocardiogram (Hewlett Packard Sonos 1000, Andover, MA, USA) and fasting blood glucose test.

Subjects were monitored for adverse events throughout the 14 day study. All participants gave written informed consent. The study protocol was approved by the local institutional review board (Biomedical Research Institute of America) and conformed to the Declaration of Helsinki.

### Assessments

Changes within and between groups' cardiovascular function as measured by Doppler echocardiograms, EKGs, blood pressure and heart rate were the primary parameters of interest. An evaluation of sleep quality was also of interest since a sympathomimetic compound was being evaluated.

An ANOVA model was used for baseline differences along with repeated measures ANOVA (RM-ANOVA) for *post hoc* analysis. Independent *t*-tests were employed to evaluate for baseline differences between the groups. Where appropriate, both Wilcoxon signed rank tests and the Mann–Whitney test were employed. An intent-to-treat approach was used in calculating the statistics. Utilizing these techniques we were able to assess both within-group changes and between group differences throughout the study period.

## Results

Among the 27 subjects who completed this study, one subject's data for her Doppler echocardiogram at day 14 was of poor quality and could not be adequately interpreted, thus her data for that particular variable has been excluded from the analysis. All the data is presented in Table 1. Baseline characteristics included: age—XEN  $40 \pm 11.4$  and PLA  $36 \pm 12.6$  y; and BMI—XEN  $31.8 \pm 4.9$ , PLA  $31.5 \pm 5.1$  kg/m<sup>2</sup>. There were 17 females and 10 males who completed the study, which was not statistically significant from baseline

Table 1

Test	Group baseline	Day 7	Day 14	P
Systolic blood pressure	XEN 120.8±10.9	118.9±10.1	118.7±9.1	NS
	PLA 123±8.8	122.5±10.6	119.3±9.1	NS
Diastolic blood pressure	XEN 76.9±8.3	75.6±7.9	76.8±6.5	NS
	PLA 75.7±6.3	76.2±8.3	75.2±10.4	NS
Heart rate	XEN 72±7.7	75.8±7.8	72.2±9.5	NS
	PLA 65±10.8	70.7±13.8	65±9.0	NS
EKGH	XEN 1	1	1	NS
	PLA 1	1	1	NS
LVEF (%)HH	XEN 61±4.8	—	62.3±4.8	NS
	PLA 61.4±3.8	—	65±4.3	NS
Total echo	XEN 1	—	1	NS
	PLA 1	—	1	NS
Fasting glucose (mg/dl)	XEN 97.5±9.3	—	93.1±11.5	NS
	PLA 91±6.9	—	92.5±4.1	NS
VAS-SQY	XEN 7.7±1.6	7.5±1.8	7.2±1.6	NS
	PLA 7.9±1.9	7.8±2.2	7.9±1.9	NS

XEN=Xenadrine® group,  $n=19$ ; PLA=placebo,  $n=8$ . HEKG scored as 1=normal or unchanged from baseline, 2=abnormal or clinically significant change. Total echo scored as 1=normal or unchanged from baseline, 2=abnormal or clinically significant change. HHLVEF=left ventricular ejection fraction. VAS-SQY=visual analog scale—sleep quality. NS=not significant (within and between groups).

( $P=0.420$ ). There were no significant differences between the treatment group and placebo for any of the cardiovascular related parameters (heart rate, blood pressure, serial EKG, or in the Doppler echocardiogram, all  $P>0.05$ ). In examining the EKGs further, there was no change in ST waves or QRS complex from baseline or between the groups. There were also no changes in heart chamber size, wall motion and valve movements or in cardiac structure as measured by the Doppler echocardiogram from baseline within or between the groups. In addition, fasting blood glucose was unchanged from baseline readings ( $P=0.265$ ). No significant change in sleep habits/quality was observed as measured by the Visual Analog Scale throughout the study period ( $P=0.427$ ).

There were no serious adverse events. Adverse events included dry mouth, 'feeling hyper', headache, increased thirst and difficulty initiating sleep. Statistically, there were no differences between treatment and placebo for adverse events.

## Discussion

Previous studies have demonstrated the herbal ephedrine and caffeine to be safe and effective for weight and fat loss.<sup>7-10</sup> This is also true for the synthetic versions.<sup>9-12</sup> However, the adverse reports reported to the United States Food and Drug Administration (FDA) cannot be ignored.<sup>1</sup> Ephedrine administration causes the release of catecholamines (via  $\alpha$ - and  $\beta$ -adrenoceptors), while caffeine has  $\alpha$ -adrenergic-like properties (phosphodiesterase enzyme inhibition), thus it impacts cardiovascular function. The commercial weight loss aid tested also contains Bitter Orange standardized for synephrine (phenylephrine); this alkaloid is also considered

to be a sympathomimetic. A recent study evaluated the cardiovascular effects of synephrine in normotensive adults and found that it did not affect hemodynamics and thus is safe.<sup>13</sup>

The aim of the present study was to evaluate the acute cardiovascular effects of the commercial weight loss aid vs placebo. In the present study, the herbal ephedrine- and caffeine-containing product had no effect over 14 days on heart rate, systolic and diastolic blood pressure, serial EKG's or Doppler echocardiograms. The tests on days 7 and 14 were done after the first dose was taken (containing 20 mg ephedra alkaloids, 200 mg caffeine, and 5 mg synephrine). These findings are in agreement with that of Waluga, except that he utilized a higher dose of ephedrine (25 mg). The importance of this study is that no untoward cardiovascular effects were observed, nor effects on perceived sleep quality. While 14 days is a short period for one to see heart valve defects, it is an appropriate amount of time to evaluate coronary vasospasm (which was one intent of the Doppler echocardiogram). Sympathomimetic agents with chronic and even acute use can cause a coronary vasospasm that is detectable by Doppler echocardiogram.<sup>14-16</sup> In this study, no such effect was found.

The pharmacological treatment of obesity is recognized as an important adjunct in long-term weight management. The use of both commercial and prescription pharmacotherapeutics to treat obesity has been controversial.<sup>17</sup> In the present study, the herbal ephedrine and caffeine product appeared to be as safe as the placebo in terms of its cardiovascular effects.

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