



CLINICAL RESEARCH STUDY

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Hemodynamic effects of ephedra-free weight-loss supplements in humans

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KEYWORDS:

Citrus aurantium;
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ABSTRACT

PURPOSE: Ephedra-free weight loss dietary supplements containing bitter orange (*Citrus aurantium*), a botanical source of the adrenergic amines synephrine and octopamine, have quickly emerged on consumer markets to replace banned ephedra products. These supplements may have some of the health risks associated with ephedra, but studies in humans are lacking. Our aim was to characterize the pharmacokinetics and cardiovascular effects of *C. aurantium* dietary supplements.

SUBJECTS AND METHODS: Ten healthy adult nonsmokers participated in a randomized, double-blind, placebo-controlled, three-arm crossover study. Single doses of *C. aurantium* (Advantra Z) containing 46.9 mg synephrine, Xenadrine EFX, a multi-component formulation containing 5.5 mg synephrine, and placebo were administered with a one-week washout.

RESULTS: Compared with placebo, Xenadrine EFX but not Advantra Z increased systolic and diastolic blood pressure with peak changes from baseline at 2 hours of 9.6 ± 6.2 mm Hg systolic ($P = 0.047$), and 9.1 ± 7.8 mm Hg diastolic ($P = 0.002$). Heart rate was increased from baseline at 6 hours compared with placebo (16.7 beats per minute with Xenadrine EFX, $P = 0.011$; 11.4 beats per minute with Advantra Z, $P = 0.031$). Dose-adjusted synephrine pharmacokinetics were similar between treatments with $t_{\max} = 90$ min, $t_{1/2} = 3.0$ hours, $V/F = 16347$ L, and $CL/F = 88.9$ L/min for Xenadrine EFX.

CONCLUSION: Ephedra-free weight loss supplements have significant cardiovascular stimulant actions, similar to ephedra. These effects are not likely caused by *C. aurantium* alone, because an eightfold higher dose of synephrine (Advantra Z) had no effect on blood pressure, but may be attributable to caffeine and other stimulants in the multi-component formulation

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Weight loss dietary supplements containing bitter orange (*Citrus aurantium*) extracts have rapidly replaced ephedra products, which were banned by the United States Food and

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Drug Administration (FDA) in April 2004 because of an association with serious adverse health effects.¹⁻⁴ In addition to *C. aurantium*, new ephedra-free supplements frequently contain proprietary combinations of various botanical stimulants, and not uncommonly, the doses of these active constituents are not quantitated on the product label.

The dried fruit peel of bitter orange, known in Chinese herbal medicine as *Zhi shi*, is a traditional remedy for gastrointestinal ailments.⁵ The known active components of

C. aurantium include the adrenergic amines synephrine, octopamine, hordenine, tyramine, and N-methyltyramine. The predominant constituents are synephrine and octopamine, which are structurally similar to norepinephrine. The pharmaceutical forms of synephrine, phenylephrine and Neosynephrine, are commonly used to treat hypotension and nasal congestion. Synephrine and octopamine also occur endogenously. Although their physiologic roles have not been fully characterized, these substances appear to interact with trace amine receptors in the brain and may be involved in the pathogenesis of migraine headaches.⁶ Peripherally, synephrine acts at α_1 -adrenergic receptors, resulting in vasoconstriction and increased blood pressure.⁷ There is some evidence that synephrine and octopamine also have β_3 -adrenergic agonist activity, which could account for purported lipolytic actions, although this has not been demonstrated in humans.⁵

Methylxanthines such as caffeine, theophylline, and theobromine occur naturally in many plants. Extracts of *Paullina cupana* (guarana), yerba mate, cocoa, and green tea are frequently found in herbal weight-loss dietary supplements. In some products, the total caffeine per dose is equivalent to as much as three to four cups of coffee. Caffeine is a central nervous system (CNS) stimulant and increases systolic blood pressure through adenosine inhibition.⁸ It is also known to enhance the effects of other sympathomimetics such as ephedrine and phenylpropanolamine.^{9,10}

Because newly re-formulated weight-loss supplements contain botanicals that possess sympathomimetic activity, there is concern that these products may pose some of the same health risks as ephedra.⁵ Few studies have been conducted on the efficacy or safety of ephedra-free dietary supplements, and little is known about the potential adverse effects of taking *C. aurantium* alone or in combination with other herbal ingredients. Although reports of adverse effects have not been conclusively linked with use of *C. aurantium* extracts, there is one published report of stroke in a 38-year-old man,¹¹ one case of exercise-induced syncope and QT prolongation in a 22-year-old woman,¹² and a possible case of myocardial infarction in a 55-year-old woman¹³ associated with use of dietary supplements containing bitter orange. Because existing surveillance systems for detecting adverse reactions to dietary supplements are not very effective,¹⁴ other cases of toxicity related to *C. aurantium* may have occurred and been unrecognized or unreported.

We are aware of just one published study of the effects of a synephrine-caffeine herbal weight loss supplement in humans.¹⁵ Although no adverse effects were reported and no increase in blood pressure was observed after six weeks of use, frequent hemodynamic monitoring was not performed. In a clinical study involving oral administration of freshly squeezed juice of *C. aurantium* to 12 normotensive adults, heart rate and blood pressure were not affected.¹⁶ However, a rodent study showed that high doses of extracts of *C. aurantium* cause ventricular arrhythmias and death.¹⁷

To date, there have been no human studies correlating acute hemodynamic effects with plasma synephrine levels after oral ingestion of weight loss products that contain *C. aurantium* extracts. In this report, we present novel data on the pharmacokinetics and cardiovascular effects of *C. aurantium* taken orally as two different dietary supplement formulations.

Methods

Clinical study

This was a randomized, double-blind, 3-arm crossover study involving 10 healthy adults aged 18 to 49 years. All volunteers gave written informed consent before study participation. The Committee on Human Research at the University of California, San Francisco (UCSF) approved the study protocol. Subject eligibility was determined by medical history, physical examination, and screening laboratory tests that included complete blood count, serum chemistry tests, urine toxicology testing for illicit drug use, and urine pregnancy testing for women. Exclusion criteria included any history of cardiac, thyroid, liver, or renal disease, hypertension, diabetes, psychiatric or seizure disorder, pregnancy or lactation, prescription or illicit drug use, cigarette smoking, and heavy use of caffeine (>3 cups of coffee or equivalent per day). Subjects were instructed to abstain from caffeine, or any over-the-counter or herbal product for 24 hours before the study.

Subjects were admitted to the General Clinical Research Center at San Francisco General Hospital on the night before testing and fasted after midnight. At 8 AM the next morning, subjects were given a single oral dose of placebo, Advantra Z (Nutratech, Inc., Wayne, NJ), or Xenadrine EFX (Cytodyne Technologies Inc., Manasquan, NJ). The product formulations and doses of active ingredients that were measured in the dietary supplements are shown in Table 1. The placebo and supplement doses were packaged in identical gelatin capsules for blinding of the research subjects, nurses, and clinical research staff. Treatment order was determined by use of an online randomization program.¹⁸ Subjects rested in their hospital room after dosing. Caffeine-free meals were given beginning 3 hours after dosing. A minimum one-week washout period occurred between the 3 study visits.

Measurements

Venous blood samples (7 mL) were collected from an indwelling forearm catheter at baseline, 30, 60, and 90 minutes, and 2, 3, 4, 6, 8, and 12 hours after dosing. The blood was centrifuged and the separated plasma was stored at -20°C for subsequent analysis of synephrine, octopamine, and caffeine concentrations. Heart rate and blood pressure were recorded with an automatic sphygmomanometer for

Table 1 Quantities of active dietary supplement ingredients determined by laboratory analysis using HPLC and GC-MS

Average amount per capsule or tablet (mg)	Xenadrine EFX*	Advantra Z†
Synephrine	2.75	15.6
Octopamine	2.96	trace
Caffeine	119.6	-
Study dose amount (mg)	2 capsules	3 tablets
Synephrine	5.5	46.9
Octopamine	5.7	trace
Caffeine	239.2	-

*Listed ingredients include: Vitamin C (100 mg), vitamin B6 (10 mg), pantothenic acid (12 mg), magnesium (10 mg), and a proprietary Thermodyne complex (1415 mg) consisting of Tyroplex (l-tyrosine, acetyl-l-tyrosine), green tea extract, Seropro (cocoa extract containing phenylethylamine, tyramine, and theobromine), yerba mate, d-methionine, ginger root, isotherm (3,3',4',5'-7 pentahydroxyflavone, 3,3',4',7-tetrahydroxyflavone), bitter orange (synephrine, n-methyltyramine, hordenine, octopamine, tyramine), DMAE (2-dimethylaminoethanol), grape seed extract. Dose amounts are not provided on product label.

†Listed ingredient: *Citrus aurantium* (10 mg synephrine per tablet).

one hour before dosing, and then before each blood draw. Questionnaires that rate physical symptoms, moods, and emotions were administered at baseline and 1, 2, and 6 hours after dosing. Subjects were instructed to rate on a 10-cm visual analog scale how they feel at the time, from zero (none) to 10 (strongest) for feeling lethargic, nauseated, shaky, heart pounding, sweating, flushed, headache, alert, able to concentrate, calm, upbeat, or irritable.

Analysis

Plasma concentrations of synephrine, octopamine, and caffeine were measured over 12 hours, and pharmacokinetic parameters of maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC), total clearance (CL/F), and apparent volume of distribution (V/F) were estimated by noncompartmental methods with use of WinNonlin (Version 3.1, Pharsight Corporation, Mountain View, Calif). AUC was calculated using the log/linear trapezoidal rule for the 12-hour postdosing period and extrapolated to infinity (0-∞). The time to reach the maximum plasma concentration, T_{max} , was estimated directly from the plasma concentration-time data.

The dietary supplements were analyzed for caffeine by GC/MS, and for synephrine and octopamine content by high-performance liquid chromatography.¹⁴ A novel tandem LC/MS-MS method developed in our laboratory to measure ephedrine alkaloids¹⁹ was modified to measure levels of synephrine and octopamine in plasma samples. This involved synthesis of a stable isotope-labeled internal standard (synephrine- d_3) and development of an extraction procedure that is suitable for synephrine and octopamine.

Briefly, the method involves precipitation of plasma proteins, addition of pH 10 buffer, and extraction with a mixture of methylene chloride, ethyl acetate, and isopropyl alcohol. The extract is evaporated, reconstituted in the HPLC mobile phase, and an aliquot is injected into the LC-MS/MS system. Atmospheric pressure chemical ionization (APCI) is used, the mass spectrometer is operated in the selected reaction-monitoring mode, and quantitation is achieved using the internal standard method, with standard curves generated using linear regression. Standard curves were linear from 1 to 100 ng/mL, and accuracy was excellent for blank plasma spiked with 5, 20, and 50 ng/mL.

Statistics

All results are expressed as means \pm standard deviations (SD) or medians \pm 95% confidence intervals (CI) in the text and tables, and, for clarity, as means \pm standard errors (SEM) in the figures. Pair-wise comparisons of changes from baseline were made between treatments at all times after dosing with paired *t*-tests, or Wilcoxon signed-ranks tests for nonparametric data. All of the data were analyzed using SAS (Version 8.2, SAS Institute, Cary, NC). Differences with a two-sided $P < 0.05$ were considered statistically significant.

Results

Five men and five women aged 19 to 42 years (mean 27 years) were enrolled and all subjects completed the study. No adverse events occurred. Subjects ranged in weight from 51.2 to 84.7 kg (mean 70.3 kg). The race/ethnicity of the subjects were white (4), African-American (2), Hispanic (2), and Asian/Pacific Islander (2).

The mean plasma concentrations of synephrine over time after dosing with Xenadrine EFX and Advantra Z are shown

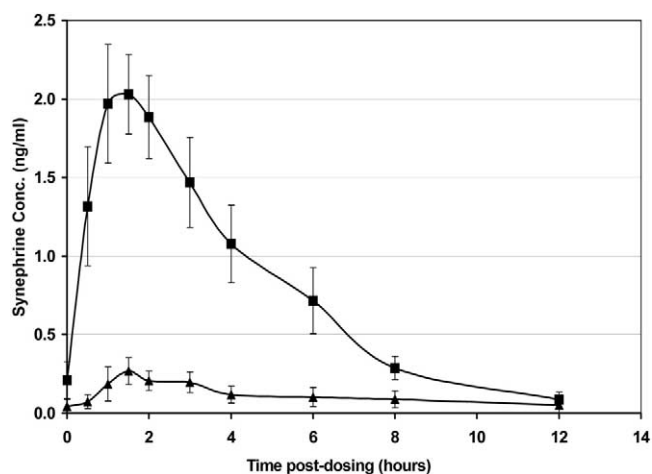


Figure 1 Plasma concentrations of synephrine over time after oral dosing with Xenadrine EFX (▲) and Advantra Z (■). Data are means \pm standard errors.

Table 2 Summary of synephrine pharmacokinetics after oral dosing with *C. aurantium*

Pharmacokinetic parameter	Xenadrine EFX	Advantra Z
T_{max} (minutes)	90	75
C_{max} (ng/mL)	0.27 ± 0.14	2.85 ± 0.86
$T_{1/2}$ (h)	3.0 ± 2.7	3.1 ± 2.2
AUC/dose (min·ng/mL·mg)	15.4 ± 9.5	14.6 ± 6.0
V/F (L)	16347 ± 6987	19141 ± 10665
CL/F (L/min)	88.9 ± 51.8	80.3 ± 33.5

Values are means \pm standard deviations, except for T_{max} , for which medians are shown.

C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; $T_{1/2}$ = elimination half-life; AUC/dose = area under the plasma concentration versus time curve extrapolated to infinity, divided by synephrine dose; V/F = apparent volume of distribution divided by bioavailability; CL/F = clearance divided by bioavailability.

in Figure 1, and the pharmacokinetic parameters for synephrine are summarized in Table 2. After correcting for dose differences, there was no significant difference in synephrine pharmacokinetics between the multi-ingredient and single-ingredient dietary supplements. With ingestion of Xenadrine EFX, mean caffeine pharmacokinetics were T_{max} 90 minutes; C_{max} 5.1 ± 1.3 $\mu\text{g/mL}$; $t_{1/2}$ 7.8 ± 3.1 hours, $AUC_{(0-\infty)}$ 66.9 ± 36.1 $\mu\text{g}\cdot\text{hour/mL}$; CL/F 75.5 ± 35.7 mL/min; V/F 42.7 ± 10.3 L. Pharmacokinetic parameters could not be estimated for octopamine because 99% of the plasma samples measured serially after dosing with Xenadrine EFX and Advantra Z were below the limit of quantitation of 0.2 ng/mL for octopamine.

As shown in Figures 2 and 3, Xenadrine EFX significantly raised mean systolic and diastolic blood pressure compared with placebo, with maximal increases observed 2 hours after ingestion. Peak changes from baseline were 9.6

± 6.2 mm Hg for systolic blood pressure ($P = 0.047$ vs placebo), and 9.1 ± 7.8 mm Hg for diastolic blood pressure ($P = 0.002$ vs placebo). Advantra Z did not raise systolic or diastolic blood pressure. Heart rate was significantly increased from baseline at 6 hours after dosing with both treatments (Figure 4), with mean values of 16.7 ± 12.4 beats per minute for Xenadrine EFX, ($P = 0.011$ vs placebo); and 11.4 ± 10.8 beats per minute for Advantra ($P = 0.031$ vs placebo).

Subjective responses to the study treatments were significant for a mean difference in alertness 2 hours after dosing with Xenadrine EFX compared with Advantra Z ($P = 0.006$). The mean score for alertness of 3.5 with Xenadrine EFX versus 1.2 with placebo approached statistical significance ($P = 0.07$). The mean alertness score for Advantra Z decreased from baseline to -0.55 at 2 hours. No other differences in subjective responses to the treatments were observed.

Discussion

In this study, we present novel data on the disposition characteristics and effects of synephrine taken orally as *C. aurantium*. We demonstrate for the first time that some ephedra-free weight-loss dietary supplements raise blood pressure in healthy, normotensive adults. These findings indicate that re-formulated weight loss supplements have similar acute cardiovascular stimulant actions as banned ephedra products and could cause adverse health effects in some individuals.

From the plasma concentration data, it appears that synephrine and octopamine are poorly absorbed or rapidly metabolized when taken orally, as the C_{max} for both drugs was less than 1 ng/mL after dosing with Xenadrine EFX. A

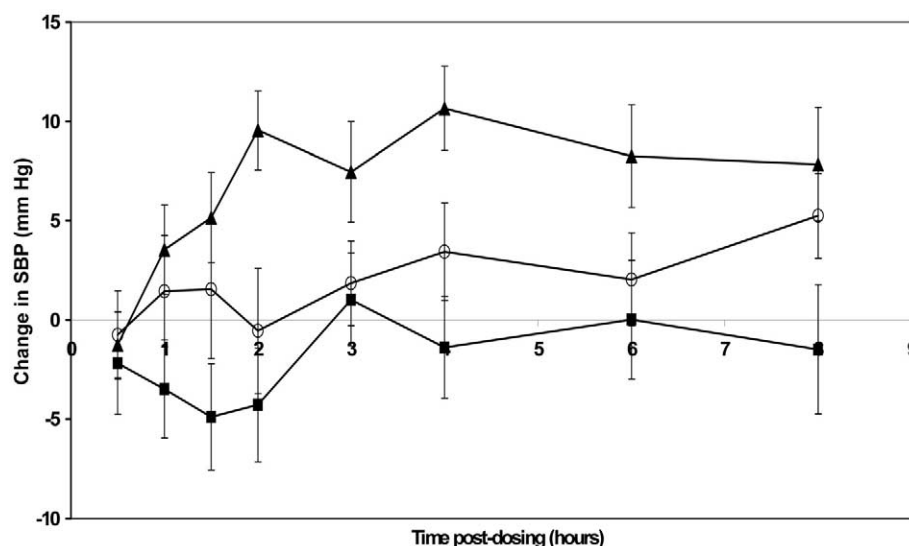


Figure 2 Change from baseline in systolic blood pressure over time after oral dosing with Xenadrine EFX (▲) and Advantra Z (■), and placebo (○). Data are means \pm standard errors. $P < 0.05$ for (▲) vs (○) at 2 hours and 4 hours.

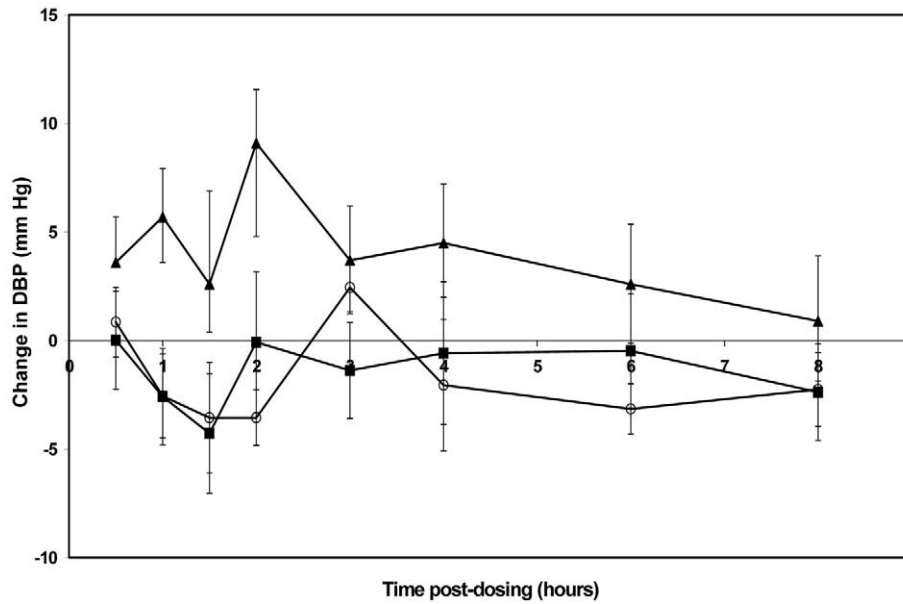


Figure 3 Change from baseline in diastolic blood pressure over time after oral dosing with Xenadrine EFX (▲) and Advantra Z (■), and placebo (○). Data are means \pm SEMs. $P < 0.05$ for (▲) vs (○) at 1 hour and 2 hours.

previous pharmacokinetic study of pharmaceutical synephrine (*Sympatol*) showed that the time to peak plasma concentration was 1 to 2 hours, and the elimination half-life was about 2 hours,²⁰ which are consistent with our findings.

Our study suggests that *C. aurantium*, when ingested alone in modest doses, is unlikely to have significant pharmacological activity. The finding that ingestion of Advantra Z, containing an eightfold higher dose of synephrine than Xenadrine EFX, had no effect on blood pressure supports this hypothesis. However, when taken as a combination product with other active herbal ingredients including caffeine, significant increases in blood pressure resulted. In previous studies, caffeine has been shown to modestly in-

crease systolic but not diastolic blood pressure.¹⁰ That both systolic and diastolic blood pressure were increased with Xenadrine EFX suggests that the vasopressive effects are not due to caffeine alone but potentially related to the actions or interactions of other constituents in the multi-ingredient product.

A transient but significant increase in heart rate was observed with both Xenadrine EFX and Advantra Z, suggesting that *C. aurantium* may have some β -1 adrenergic activity. A previous investigation that involved oral administration of 20 mg/kg *C. aurantium* extract to rats resulted in ventricular tachycardia and widening of the QRS interval; and in another study involving guinea pigs, synephrine had

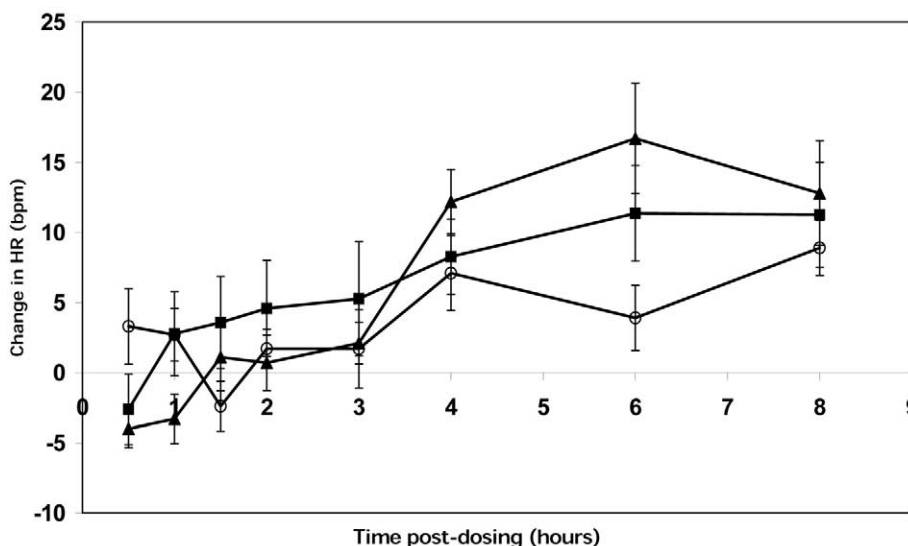


Figure 4 Change from baseline in heart rate over time after oral dosing with Xenadrine EFX (▲) and Advantra Z (■), and placebo (○). Data are means \pm standard errors. $P < 0.05$ for (▲) and (■), vs (○) at 6 hours.

positive chronotropic activity on atrial tissue. These findings indicate that additional human studies of the effects of *C. aurantium* on cardiac electrophysiology are needed.

The lack of significant subjective reports of mood and emotional responses to the treatments suggests that *C. aurantium* does not have pronounced psychoactive stimulant actions, which may indicate that synephrine has poor CNS penetration. Only Xenadrine EFX resulted in an increased score for alertness, which is likely attributable to the CNS stimulant effects of caffeine.¹⁰

Whether dietary supplements that contain *C. aurantium* result in increased lipolysis, accelerated metabolic rate, or decreased appetite was not the focus of this study. As with any drug, a risk-benefit analysis is needed to determine if any potential advantage for weight loss outweighs the possible adverse effects of the product. Chronic dosing studies are needed to determine if the acute hemodynamic effects seen with Xenadrine EFX persist or diminish with repeated use. Until such data are available, physicians should caution patients about the use of ephedra-free weight-loss dietary supplements and monitor blood pressure in those who choose to use these supplements. Individuals with hypertension, heart disease, or other pre-existing conditions that could be exacerbated by the sympathomimetic effects of botanical stimulants should avoid use of these products.

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