International Journal of Obesity (2002) 26, 593–604
 0307–0565/02 $25.00
www.nature.com/ijo

PAPER

Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial

CN Boozer[1]*, PA Daly[2], P Homel[3], JL Solomon[1], D Blanchard[2], JA Nasser[1], R Strauss[4] and T Meredith[5†]

[1]*New York Obesity Research Center, St Luke's-Roosevelt Hospital and Columbia University, New York, USA;* [2]*Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA;* [3]*Beth Israel Medical Center, New York, USA;* [4]*Cigna Health Care, Los Angeles, California, USA; and* [5]*Vanderbilt University Medical Center, Nashville, Tennessee, USA*

OBJECTIVE: To examine long-term safety and efficacy for weight loss of an herbal Ma Huang and Kola nut supplement (90/192 mg/day ephedrine alkaloids/caffeine).
DESIGN: Six-month randomized, double-blind placebo controlled trial.
SUBJECTS: A total of 167 subjects (body mass index (BMI) $31.8 \pm 4.1\,kg/m^2$) randomized to placebo ($n = 84$) or herbal treatment ($n = 83$) at two outpatient weight control research units.
MEASUREMENTS: Primary outcome measurements were changes in blood pressure, heart function and body weight. Secondary variables included body composition and metabolic changes.
RESULTS: By last observation carried forward analysis, herbal *vs* placebo treatment decreased body weight (-5.3 ± 5.0 *vs* -2.6 ± 3.2 kg, $P < 0.001$), body fat (-4.3 ± 3.3 *vs* -2.7 ± 2.8 kg, $P = 0.020$) and LDL-cholesterol (-8 ± 20 *vs* 0 ± 17 mg/dl, $P = 0.013$), and increased HDL-cholesterol ($+2.7 \pm 5.7$ *vs* -0.3 ± 6.7 mg/dl, $P = 0.004$). Herbal treatment produced small changes in blood pressure variables ($+3$ to -5 mmHg, $P \leq 0.05$), and increased heart rate (4 ± 9 *vs* -3 ± 9 bpm, $P < 0.001$), but cardiac arrhythmias were not increased ($P > 0.05$). By self-report, dry mouth ($P < 0.01$), heartburn ($P < 0.05$), and insomnia ($P < 0.01$) were increased and diarrhea decreased ($P < 0.05$). Irritability, nausea, chest pain and palpitations did not differ, nor did numbers of subjects who withdrew.
CONCLUSION: In this 6-month placebo-controlled trial, herbal ephedra/caffeine (90/192 mg/day) promoted body weight and body fat reduction and improved blood lipids without significant adverse events.
International Journal of Obesity (2002) **26,** 593–604. DOI: 10.1038/sj/ijo/0802023

Keywords: Ma Huang; Kola nut; ephedrine; ephedra alkaloids; obesity; weight loss; clinical trial; herbal medicine; alternative medicine

Introduction

Since passage of the Dietary Supplement Health and Education Act (DSHEA) by Congress in 1994, classifying herbal compounds as 'dietary supplements', marketing of such products in the USA has escalated. Sales are estimated to have risen from $9.8 billion in 1995 to $14.7 billion in 1999.[1] A large portion of that market is devoted to herbal dietary supplements containing ephedra, with three billion servings reportedly sold[2] and approximately 12 million individuals estimated to be using such products in 1999.[2] While the consequence of DSHEA is that the Food and Drug Administration (FDA) does not regulate the sales of these products, the FDA does collect anecdotal reports of adverse events and these reports have raised concerns about the safety of ephedra products by the FDA[3] and the media.[1,4,5]

A major reason for use of ephedra-containing herbal products is body weight reduction. Questions of safety and efficacy are central issues for any agent used for human weight control. Ephedrine, the primary active ingredient of herbal ephedra, has been well studied both alone, and in combination with caffeine. Placebo-controlled studies have demonstrated that ephedrine, particularly in combination

*Correspondence: CN Boozer, New York Obesity Research Center, WH 1029, St Luke's-Roosevelt Hospital Center, 1111 Amsterdam Avenue, New York, NY 10025, USA.
E-mail: cnb7@columbia.edu
†Current address: World Health Organization, Geneva, Switzerland.
Received 26 October 2001; revised 6 February 2002; accepted 11 February 2002

with caffeine, is effective in promoting weight loss without increasing serious adverse events[6–9] and the combination is used for that purpose in Europe.[10] Despite this literature for synthetic ephedrine, the lack of data demonstrating similar effects for herbal ephedra has contributed to questions of both its safety and efficacy.[2]

Two clinical trials demonstrating efficacy of herbal ephedra combinations for reduction of body weight and fat have been completed.[11,12] Both studies, however, were only 8 weeks in duration, thus limiting conclusions about longer-term safety. The purpose of the present 6 month study was to provide objective assessment of safety and efficacy for weight-loss of a herbal dietary supplement containing Ma Huang herbal ephedra and Kola nut (as sources of ephedrine alkaloids and caffeine). While the emphasis of the present investigation was on the detailed monitoring of blood pressure, heart rate and disrhythmias during the acute phase of treatment, this study is also the first reported long-term, clinical trial of a herbal preparation containing ephedrine alkaloids and caffeine in combination.

Methods

Study design

The study was a prospective, two-arm, 6-month, randomized, double-blind, placebo-controlled, clinical safety and efficacy trial conducted at two sites (New York and Boston). Efficacy was assessed by measuring changes in body weight, body fat and waist and hip circumferences. Safety was assessed by determining changes in cardiovascular parameters, blood chemistries, liver enzymes, self-reported symptoms and reasons for withdrawal from the study.

Randomization of equal numbers of subjects to placebo or herbal groups was achieved using a random number table, with block sizes varying between two and eight. A statistician not involved in the study produced separate randomization codes for the two sites. Sealed copies of these codes were provided to the investigators for emergency identification. Otherwise, codes remained sealed until completion of the study, when another statistician, who was not involved in carrying out the study, was provided with the code and the data for analysis.

Statistical analyses were designed on an 'intention-to-treat' basis to achieve a statistical power of 0.90 and a 0.05 type I error for a two-sided test. Power calculations were primarily concerned with the possibility of adverse effects during the acute phase of the study (weeks 1–4). Using a two-sample *t*-test, a minimum of 66 subjects in each group would have been sufficient to detect a difference of 4.1 mmHg systolic blood pressure (s.d. = 7.23), a difference of 4.6 mmHg diastolic blood pressure (s.d. = 6.0), and also a difference in heart rate of 6 bpm (s.d. = 10.36). The study was approved by the Institutional Review Boards of St Luke's-Roosevelt Hospital Center in New York and Beth Israel Deaconess Medical Center in Boston and all subjects gave written consent prior to participation.

Subjects

Subjects, recruited by advertisements in local newspapers and flyers, were interviewed by telephone. Eligibility requirements included age between 18 and 80 y and body mass index (BMI) ≥ 25 and $\leq 40\,kg/m^2$. Subjects were recruited without regard to racial or ethnic background. Smokers were not excluded, nor were diabetics with reasonable control (hemoglobin A1C $\leq 7.8\%$) who did not take insulin or oral diabetic medication. Subjects were excluded if they were not otherwise healthy, were pregnant or nursing, had recently lost weight or participated in other diet or drug studies, or if they reported consumption of > 500 mg/day caffeine (see Appendix I for complete list of exclusions).

For inclusion in the study, subjects were required to successfully pass a medical screening by a study physician. This included medical history and symptom evaluations, a physical examination that included measurement of height and weight, sitting blood pressure and pulse rate, an EKG and a laboratory evaluation including blood test and urine toxicology screen. Subjects were not included if blood pressure was $\geq 140/90$ or if values from laboratory tests were outside normal ranges. Screening also included 24 h measurement of blood pressure by ambulatory blood pressure monitor (ABPM) and heart rhythm by Holter monitor. Subjects were excluded if monitoring detected hypertension (defined as mean 24 h systolic BP ≥ 139 mmHg or mean 24 h diastolic BP ≥ 87 mmHg) or significant ventricular ectopy (including > 1000 premature beats/24 h, 'R on T' phenomenon, torsades de pointes, or QT interval prolongation; runs of supraventricular tachycardia > 1 min, or new onset atrial fibrillation; or presence of any other clinically significant rhythm disturbance). Holter data and EKGs of subjects with multiform or multifocal ventricular events (MFVE) were reviewed by the study cardiologist prior to admission. Those without evidence of other significant cardiac disease were allowed to enroll in the study.

Following successful medical screening, subjects returned within 1–4 weeks for a baseline evaluation that included repeat measurements of height, weight, sitting blood pressure and heart rate as well as measurement of waist and hip circumferences and body fat. The symptom questionnaire was again completed and ABPM and Holter monitors worn for a second 24 h period. Subjects who did not fall into any of the exclusion categories after these baseline measures were randomized to either placebo or the herbal preparation (Ma Huang/Kola nut).

Treatment

At randomization, subjects were counseled to eat normally, but limit intake of dietary fat to 30% of calories and to exercise moderately (eg walking 30 min/day, three times a week). Handouts on good eating habits and a progressive walking/exercise program were provided. Active and placebo tablets were supplied in opaque white plastic bottles containing a known number of tablets. Subjects were directed to take

two tablets, 30 min before each meal, three times a day (six tablets per day, the maximum amount recommended on most ephedra-containing commercial products) and to return unused pills, which were counted to determine adherence.

The active preparation was a herbal mixture (provided by Science, Toxicology and Technology, San Francisco, CA, USA) containing Ma Huang (NutraTech Inc, Gardena, CA, USA) and Kola nut (Ashland Distribution Corp, Santa Anna, CA, USA) as the only active ingredients. Each tablet was specified to contain 15 mg of total ephedrine alkaloids and 32 mg of caffeine per tablet, for a total daily amount of ephedrine alkaloids and caffeine of 90 and 192 mg, respectively. The placebo was an identical appearing tablet containing inert ingredients. Certificates of analyses for ephedrine alkaloid and caffeine content provided to the supplier were validated by the investigators.

During the initial month of treatment, subjects returned weekly to pick up pills, review dietary and exercise advice, complete the symptom questionnaires and have weight, sitting blood pressure and pulse rate measured. At weeks 1, 2 and 4, ABPM and Holter monitors were worn for additional 24 h periods. At the end of the first month, another blood sample was taken for assessment of ALT, creatinine and HCG (in women of child-bearing age).

During the subsequent 20 weeks, subjects returned every 4 weeks for a 30 min visit. The symptom questionnaire was completed, and a brief dietary and symptom review and physical evaluation by the study coordinator including weight, sitting blood pressure and heart rate was taken. Blood was taken for ALT, creatinine and HCG (in women of child-bearing age) at each of these visits.

At week 12 and 24 (final) visits, additional fasting blood samples were taken, EKGs recorded, and measurements of waist and hip circumferences and body fat content repeated.

Measurements

Medical and nutrition history and self-reported symptoms were evaluated by questionnaires designed by the investigators (PAD & TM) for this study. Height was measured to the nearest 0.5 cm by stadiometer (Holtain, Crosswell, Wales, UK). Body weight was measured to the nearest 0.1 kg using a digital scale (NY site: Weight Tronix, New York, USA; Boston site: Detecto-Medic, Detecto Scales Inc, Brooklyn, NY, USA). Trained personnel measured waist and hip circumferences at standard anatomical locations.[13] Total body fat was assessed by bioimpedance (Tanita Inc: TBF 310, Arlington Heights, IL, USA). Siri's two-compartment model was used to convert measured body density to fat.[14]

Blood studies included serum glucose and lipids (cholesterol and triglycerides), liver and renal function tests (creatinine, ALT and AST), TSH, standard electrolytes, a complete blood count (NY site: Quest Diagnostic Laboratory, Teterboro, NJ, USA; Boston site: Veterans Admistration North Texas Health Care System, Dallas, TX, USA). Toxicologic urine screens (see Appendix II for list of tests) were performed by Diagnostic Laboratories, Vanderbilt University Medical Center, Nashville, TN, USA.

Data from Holter and ABPM monitors were analyzed by Space Laboratories (Seattle, OR, USA), with follow-up evaluations as required by the study cardiologist. EKGs of the NY subjects were evaluated for four intervals (RBR, P-R, QT_C, QRS), QRS amplitude and cardiac rhythm.

Three independent laboratories (Alpha Chemical and Biomedical Laboratories, Petaluma, CA, USA; Industrial Laboratories Company Inc, Denver, CO, USA; and San Rafael Chemical Services, Salt Lake City, UT, USA) analyzed samples of active and placebo tablets by high pressure liquid chromatography (HPLC) for ephedrine, total ephedrine alkaloids and caffeine.

Statistical methods

Values are presented in the text and tables as mean ± standard deviation (s.d.) and in the figures as means ± standard errors (s.e.). The tables show statistical comparisons between the groups by the 'last observation carried forward' (LOCF) method for dealing with missing data. Values for subjects who dropped out after the acute phase (week 4) were carried forward to each subsequent time point in the trial. Figures present analyses of only data that was actually available for subjects at each time point, with no values carried forward for subjects who dropped out.

Effect of treatment on weight, body fat, waist and hip circumferences, sitting blood pressure, heart rate and blood chemistries were assessed by using a repeated measures ANOVA test for group by time interaction, followed by pair-wise *t*-tests. Repeated categorical data (eg cardiac arrhythmias) were analyzed using a weighted least squares model (WLS)[15] followed by pair-wise chi-square tests, where possible. Reasons for withdrawal in each group were compared using chi-square tests. All analyses were conducted using a two-tailed 0.05 alpha level.

Results

Subject disposition

Of 284 subjects who appeared eligible by telephone screen, 167 were randomized (83 to ephedra/caffeine and 84 to placebo; Figure 1). Of those not randomized, most either chose not to participate (45) or were ineligible due to violations of protocol inclusion requirements (15) or non-compliance with protocol requirements (8). Thirty-one were ineligible for medical reasons that were exclusionary for the protocol.

During the first 4 weeks of the study, the acute phase, 17 (20%) randomized subjects withdrew from each group, with 66 remaining in the herbal group and 67 remaining in the placebo group. During the remaining 5 months of the study, there were 20 (24%) withdrawals from the herbal group and 26 (31%) from the placebo group.

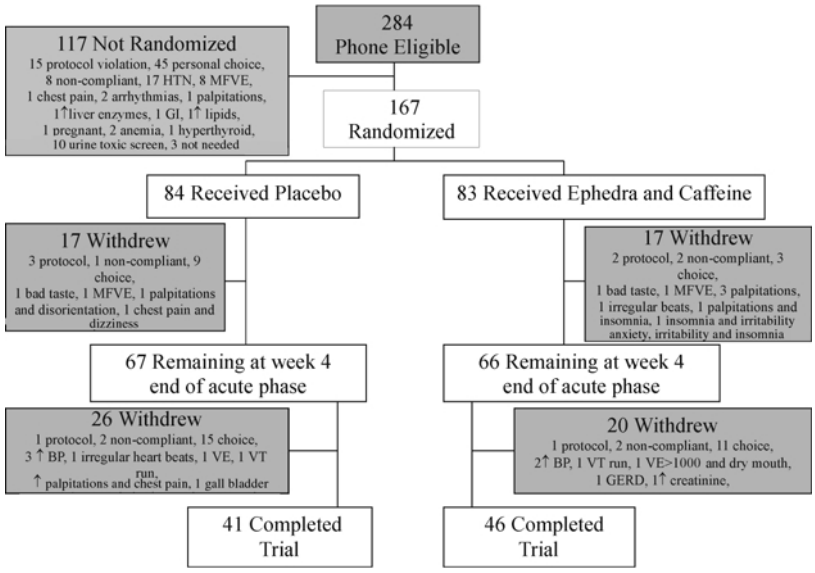

Figure 1 Disposition of all subjects recruited for the study.

Baseline physical characteristics of subjects

Subjects in the two treatment groups (P, placebo: H, herbal) did not differ ($P > 0.05$) initially in age (46.0 ± 12.2 (mean $\pm$ s.d.); 44.5 ± 12.4 y), body weight (88.1 ± 14.8; 87.9 ± 13.9 kg), or BMI (31.7 ± 4.0; 31.8 ± 4.4 kg/m^2; Table 1). Distributions of gender and self-identified race were also not significantly different between groups (P, 86% female; H, 78% female; (P, 70% Caucasian, 15% African-American and 7% Hispanic; H, 69% Caucasian, 11% African-American and 12% Hispanic).

Herbal analysis

Independent laboratory HPLC analysis detected, per placebo tablet, less than 0.3 mg (range, non-detectable to < 0.3 mg) each of caffeine and total ephedrine alkaloids and, per herbal tablet, 32.7 ± 1.5 mg caffeine and 14.4 ± 1.6 mg total ephedrine alkaloids.

Table 1 Baseline characteristics of all randomized subjects

Characteristic	*Placebo* (n = *84*)	*Herbal* (n = *83*)
Gender		
Men (*n* (%))	12 (14%)	18 (22%)
Women (*n* (%))	72 (86%)	65 (78%)
Race (*n* (%))		
Caucasian	59 (70%)	57 (69%)
African-American	13 (15%)	9 (11%)
Hispanic	6 (7%)	10 (12%)
Indian, Asian, Other	5 (6%)	6 (7%)
	X $\pm$ *s.d.*	*X* $\pm$ *s.d.*
Age (y)	46.0 ± 12.2	44.5 ± 12.4
Weight (kg)	88.1 ± 14.8	87.9 ± 13.8
Body mass index (kg/m^2)	31.7 ± 4.0	31.8 ± 4.4

Race was by self-identification. One subject in each group did not identify race.

Adherence

Adherence, calculated as the percentage of pills not returned by the subject relative to the number of pills supplied, did not differ between groups (P, $90 \pm 11\%$; H, $89 \pm 10\%$).

Treatment effects

Body weight and body composition. Results of LOCF analyses of physical values are shown in Table 2. Both treatment groups lost significant ($P < 0.001$) amounts of body weight and body fat over the 6 months of the study. Losses in the herbal group, however, were greater than in the placebo for both body weight (H, -5.3 ± 5.0; P, -2.6 ± 3.2 kg; $P < 0.001$) and body fat (H, -4.3 ± 3.3 kg, P, -2.7 ± 2.8 kg, $P = 0.020$).

Both groups also had significant decreases in waist (P, -2 ± 6 cm, $P = 0.004$ and H, -6 ± 5 cm, $P < 0.001$) and hip circumferences (P, -4 ± 4 cm, $P < 0.001$ and H, -6 ± 5, $P < 0.001$), but again these changes were significantly greater in the herbal *vs* the placebo group for both waist ($P = 0.005$) and hip circumferences ($P = 0.018$). There were no significant interactions or differences between the treatment groups in waist–hip ratio (not shown).

Mean values for all subjects for whom data were collected at each time point are shown for body weight in Figure 2 and for body fat in Figure 3. Of subjects who completed the 6-month study, those in the herbal group lost significantly more body weight than those in the placebo group (P, -3.1 ± 4.0; H, -7.0 ± 4.3 kg; $P < 0.001$). Body fat was also significantly decreased by herbal treatment for subjects with

Table 2 LOCF analysis of physical values[a]

Measure	*Study period*	*Group*		
		Placebo X ± s.d. (P-value)[b]	*Herbal X ± s.d. (P-value)*[b]	P[c]
Body weight (kg)	Baseline	87.9 ± 13.9	88.1 ± 14.8	0.955
	6 month	85.3 ± 14.7	82.8 ± 15.4	0.319
	Change	− 2.6 ± 3.2 (< 0.001)	− 5.3 ± 5.0 (< 0.001)	< 0.001
	ANOVA	Time × group interaction: $P < 0.001$		
Body fat mass (kg)	Baseline	34.2 ± 9.9	32.6 ± 9.1	0.451
	6 month	31.5 ± 10.6	28.2 ± 9.2	0.150
	Change	− 2.7 ± 2.8 (< 0.001)	− 4.3 ± 3.3 (< 0.001)	0.020
	ANOVA	Time × group interaction: $P < 0.020$		
Waist circumference (cm)	Baseline	98 ± 12	97 ± 13	0.699
	6 month	96 ± 13	92 ± 13	0.135
	Change	− 2 ± 6 (0.004)	− 6 ± 5 (< 0.001)	0.005
	ANOVA	Time × group effect: $P = 0.004$		
Hip circumference (cm)	Baseline	117 ± 10	115 ± 9	0.270
	6 month	113 ± 10	109 ± 10	0.033
	Change	− 4 ± 4 (< 0.001)	− 6 ± 5 (< 0.001)	0.018
	ANOVA	Time × group effect: $P = 0.044$		
Systolic blood pressure (mmHg)	Baseline	120 ± 11	119 ± 11	0.877
	6 month	120 ± 12	118 ± 12	0.405
	Change	0 ± 11 (0.659)	− 1 ± 9 (0.289)	0.313
	ANOVA	Time × group interaction: $P = 0.177$		
Diastolic blood pressure (mmHg)	Baseline	79 ± 8	77 ± 8	0.365
	6 month	79 ± 9	78 ± 9	0.397
	Change	0 ± 8 (0.729)	< 1 ± 8 (0.836)	0.928
	ANOVA	Time × group interaction: $P = 0.128$		
Heart rate (bpm)	Baseline	74 ± 7	69 ± 8	0.001
	6 month	71 ± 9	73 ± 10	0.130
	Change	− 3 ± 9 (0.008)	4 ± 9 (0.001)	< 0.001
	ANOVA	Time × group interaction: $P < 0.001$		

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day ($n = 69$/group for weight, SBP, DBP, heart rate; $n = 38$ for placebo and 39 for herbal for body fat; $n = 48$ for placebo and 47 for herbal for waist and hip).
[b]*P*-value for within-group change from baseline compared by paired samples *t*-test.
[c]Treatment *vs* placebo groups were compared by ANOVA test for group × time interaction followed by pair-wise *t*-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.

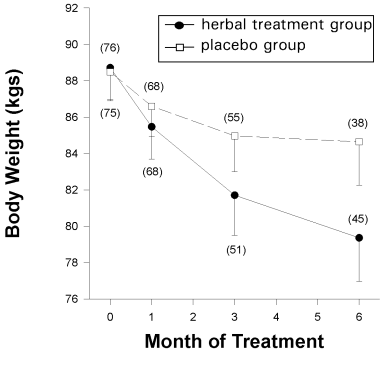

Figure 2 Effect of herbal and placebo treatment on change in body weight. Values shown include all subjects in herbal and placebo treatment groups for whom there was data at each time point (*n*).

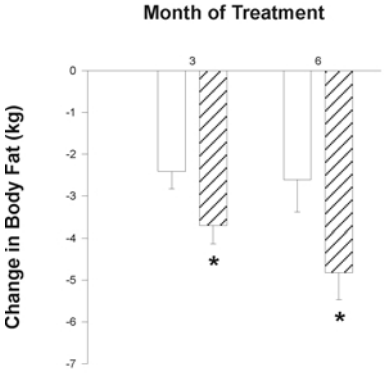

Figure 3 Change in body fat from baseline after 3 months and 6 months of herbal or placebo treatment. Open bars represent placebo ($n = 38$ at 3 months, $n = 25$ at 6 months). Hatched bars represent herbal treatment ($n = 39$ at 3 months, $n = 26$ at 6 months). *$P \leq 0.05$.

complete body composition data at 3 months (P, -2.4 ± 2.6 kg; H, -3.7 ± 2.6 kg, $P=0.031$) and 6 months (P, -2.6 ± 3.9 kg; H, -4.8 ± 3.2 kg, $P=0.032$).

Blood pressure and heart rate at office visits. Mean systolic and diastolic blood pressure measurements did not differ between treatment groups at any time point, nor was there a significant group-by-time interaction for either variable, whether analyzed by LOCF (Table 2) or using all available data (not shown). Change in heart rate was significantly different ($P<0.001$) between groups (P, -3 ± 9, $P=0.008$; H, 4 ± 9, $P<0.001$). Time-by-group interaction was also significant ($P<0.001$), with values in the herbal group compared with placebo that were lower at baseline (by 4 ± 3.9 bpm, $P=0.001$), but not significantly different (4 bpm ±3.9, $P=0.130$) at 6 months (Table 2, LOCF). Analysis of all available data for heart rate showed similar results to LOCF analysis, with a significant time-by-group interaction ($P<0.001$), and differences between groups that were significant only at baseline (when H was lower than P, $P<0.01$) and at 3 months (when H was higher than P, $P<0.05$; not shown).

Treatment groups did not differ in EKG data, analyzed at the NY site, for any of the four intervals evaluated (RR, P-R, QTc, QRS) or for QRS amplitude and heart rhythm (not shown).

Blood pressure by 24 h monitor. Data from 24 h monitors at baseline, and weeks 1, 2 and 4 were compared for 24 h mean, daytime mean (6:00 am to midnight) and night-time mean (midnight to 6:00 am), for SBP, DBP, minimum SBP and DBP, maximum SBP and DBP and mean arterial pressure (Table 3).

Effects of herbal treatment on blood pressure were small, but time-by-group interactions were statistically significant ($P\leq0.05$) for: 24 h averages of SBP, DBP and minimum SBP; and for daytime averages of SBP and minimum SBP. Maximum increases over baseline at 4 weeks in the herbal group

Table 3 Twenty-four-hour ambulatory blood pressure monitor data

		24 h average			*Day (6:00 am – midnight)*			*Night (midnight – 6:00 am)*		
		Placebo	*Herbal*	P	*Placebo*	*Herbal*	P	*Placebo*	*Herbal*	P
SBP (mmHg)	B	118±8	120±8	0.403	120±8	121±8	0.602	108±8	110±9	0.179
	W1	118±8	118±8	0.754	120±9	119±10	0.462	108±10	110±11	0.230
	W2	116±8	118±8	0.133	118±8	120±8	0.251	106±9	111±10	0.005
	W4	116±11	120±9	0.020	118±11	121±8	0.060	107±10	111±10	0.014
	ANOVA	Time×group interaction: $P=0.016$			Time×group interaction: $P=0.021$			Time×group interaction: $P=0.152$		
DBP (mmHg)	B	72±7	72±6	0.887	74±7	73±6	0.252	63±6	63±7	0.991
	W1	72±10	72±7	0.637	74±7	73±6	0.340	64±8	65±8	0.646
	W2	71±10	73±7	0.200	74±7	74±6	0.895	63±7	64±9	0.193
	W4	71±11	75±8	0.056	74±8	76±11	0.251	61±10	65±10	0.015
	ANOVA	Time×group interaction: $P=0.020$			Time×group interaction: $P=0.053$			Time×group interaction: $P=0.066$		
MINSBP (mmHg)	B	95±7	95±8	0.766	98±8	98±8	0.454	98±8	99±10	0.277
	W1	94±9	95±10	0.729	98±11	98±11	0.991	97±10	100±11	0.160
	W2	91±9	95±9	0.030	95±11	99±10	0.035	94±10	99±10	0.004
	W4	93±10	97±10	0.012	96±12	101±10	0.021	96±10	100±11	0.043
	ANOVA	Time×group interaction: $P=0.008$			Time×group interaction: $P=0.017$			Time×group interaction: $P=0.257$		
MINDBP (mmHg)	B	50±6	49±8	0.400	53±7	53±8	0.798	52±7	54±8	0.263
	W1	52±7	49±9	0.116	54±7	54±10	0.819	54±8	55±8	0.695
	W2	51±6	50±10	0.606	54±7	54±8	0.917	52±7	52±9	0.884
	W4	50±7	51±9	0.576	54±8	55±8	0.552	52±7	54±9	0.323
	ANOVA	Time×group interaction: $P=0.089$			Time×group interaction: $P=0.868$			Time×group interaction: $P=0.652$		
MAXSBP (mmHg)	B	143±12	143±11	0.741	142±12	143±11	0.922	119±9	122±11	0.077
	W1	142±13	141±12	0.917	141±13	141±12	0.713	119±12	121±13	0.370
	W2	140±12	141±10	0.591	140±12	141±10	0.835	117±12	121±13	0.046
	W4	140±14	140±13	0.716	140±14	138±21	0.559	118±12	122±12	0.078
	ANOVA	Time×group interaction: $P=0.941$			Time×group interaction: $P=0.803$			Time×group interaction: $P=0.683$		
MAXDBP (mmHg)	B	93±8	93±10	0.969	93±9	93±9	0.991	72±8	73±10	0.859
	W1	94±11	92±8	0.104	94±12	92±7	0.156	75±10	74±7	0.339
	W2	92±8	92±10	0.885	92±8	91±8	0.388	73±9	73±8	0.991
	W4	94±12	93±8	0.576	94±12	92±8	0.295	73±10	76±10	0.044
	ANOVA	Time×group interaction: $P=0.433$			Time×group interaction: $P=0.605$			Time×group interaction: $P=0.059$		
MAP (mmHg)	B	87±6	87±6	0.877	90±6	90±6	0.537	79±6	79±7	0.649
	W1	86±7	86±6	0.452	90±8	89±8	0.697	80±8	80±7	0.987
	W2	85±7	85±6	0.920	89±7	89±5	0.981	78±8	80±7	0.134
	W4	85±8	86±7	0.473	89±9	90±6	0.494	78±8	80±8	0.076
	ANOVA	Time×group interaction: $P=0.271$			Time×group interaction: $P=0.452$			Time×group interaction: $P=0.175$		

SBP, systolic blood pressure; DBP, diastolic blood pressure; MINSBP, minimum systolic blood pressure; MINDBP, minimum diastolic blood pressure. MAXSBP, maximum systolic blood pressure; MAXDBP, maximum diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. S, Screen (prior to treatment); B, baseline (prior to treatment); W1, W1, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n=67$) or placebo (P, $n=66$).

were 3 mmHg (day DBP, day min SBP, both $P=0.02$) and significant ($P \leq 0.05$) decreases occurred in max SBP for both 24 h and day averages (-3 and -5 mmHg). Most of the differences in change over time were due to decreases in the placebo group, with small or no change in the herbal group. There were no statistically significant time-by-group interactions for minimum DBP, for maximum SBP or DBP or for mean arterial pressure.

Holter monitor data. As shown by office visit measurements, there was a significant time-by-group interaction ($P=0.020$) for heart rate assessed by Holter monitor. Between-group differences were significant ($P<0.05$) only at baseline, when the heart rate of the herbal group was lower by 3 bpm (Table 4). Heart rate over the 4 weeks of Holter measurement increased by 1 ± 14 bpm in the herbal group *vs* a decrease of 5 ± 13 bpm in the placebo group ($P=0.026$).

None of the cardiac arrhythmias assessed were increased by herbal treatment. The only significant time-by-group interaction ($P<0.024$), for percentage of subjects displaying incidents of bradycardia (≤ 60 bpm) was due to a decrease in the herbal group (-12%, *vs* no change in the placebo group). Ventricular events/h did not differ between groups at any time point, nor did the percentage of subjects with tachycardia (≥ 100 bpm), MFVEs or runs of ventricular events.

Blood chemistries. By LOCF analysis, there were statistically significant 6-month improvements with herbal treatment in serum levels of total cholesterol (-6 ± 23 mg/dl, $P=0.03$), LDL-cholesterol (-8 ± 20 mg/dl), HDL-cholesterol ($+3\pm6$, $P=0.0001$), and triglycerides (-12 ± 41 mg/dl, $P=0.01$), with no change in blood glucose (0 ± 10 mg/dl, $P=0.68$; Table 5). These changes were significantly different from placebo, however, only for LDL-cholesterol, HDL-cholesterol and glucose. The difference in change in serum levels

Table 4 LOCF analysis of Holter monitor data

		Group		
Measure	*Study period*	*Placebo*	*Herbal*	P
Pulse, average bpm/24 h ± s.d.	Baseline	78 ± 8	75 ± 11	0.050
	Week 1	74 ± 10	77 ± 12	0.169
	Week 2	74 ± 10	77 ± 12	0.211
	Week 4	73 ± 12	76 ± 14	0.370
	ANOVA	Time×group interaction: $P=0.020$		
Ventricular events/h, median (inter-quartile range)	Baseline	0.08 (0.57)	0.06 (0.14)	0.188
	Week 1	0.04 (0.29)	0.00 (0.13)	0.129
	Week 2	0.06 (0.44)	0.04 (0.29)	0.400
	Week 4	0.04 (0.36)	0.04 (0.16)	0.250
Ventricular couplets (%)	Baseline	3.08%	2.94%	1.0
	Week 1	3.08%	5.88%	0.68
	Week 2	3.08%	8.82%	0.27
	Week 4	13.85%	4.41%	0.07
	WLS	Time×group interaction: $P=0.061$		
Runs ventricular events (%)	Baseline	0.00%	2.26%	0.237
	Week 1	3.08%	0.00%	0.237
	Week 2	1.54%	2.94%	1.000
	Week 4	1.54%	0.00%	0.489
Multifocal ventricular events (%)	Baseline	33%	25%	0.288
	Week 1	27%	19%	0.263
	Week 2	27%	29%	0.784
	Week 4	35%	25%	0.213
	WLS	Time×group interaction: $P=0.369$		
Bradycardia (%)	Baseline	83%	92%	0.101
	Week 1	83%	72%	0.216
	Week 2	89%	78%	0.103
	Week 4	83%	80%	0.681
	WLS	Time×group interaction: $P=0.024$		
Tachycardia (%)	Baseline	97%	100%	0.151
	Week 1	100%	100%	
	Week 2	100%	98%	0.319
	Week 4	100%	100%	

Pulse analyzed by ANOVA followed by pair-wise *t*-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.
Ventricular events reported as median (inter-quartile range); analyzed by Wilcoxon/Mann–Whitney non-parametric test.
Ventricular couplets, MFVEs, bradycardia and tachycardia reported as percentage of subjects, analyzed by WLS.
Runs of ventricular events and tachycardia reported as percentage (WLS not permitted because of 0 values).

of glucose was due to a significant increase in the placebo group (3 ± 9 mg/dl, $P = 0.02$).

As with the LOCF analyses, analysis of changes in serum levels of blood lipids and glucose of all subjects for whom there was complete data found significant differences for P *vs* H for LDL-cholesterol (-0.8 ± 24.2 *vs* -12.9 ± 23.1 mg/dl, $P = 0.026$), HDL-cholesterol (-0.5 ± 9.4 *vs* 4.4 ± 6.6 mg/dl, $P = 0.011$) and glucose (5.3 ± 12.1 *vs* -0.8 ± 12.8 mg/dl, $P = 0.036$; data not shown). Differences between groups for changes in serum triglycerides and total cholesterol were not significantly different ($P > 0.05$).

There were no significant changes or differences between the two groups at any time point for serum levels of any of the electrolytes measured, or for ALT, AST, or creatinine (data not shown).

Symptoms. Analysis of self-reported symptoms is shown in Table 6. The symptoms that subjects reported to be most consistently increased by the herbal *vs* the placebo treatment were dry mouth, heartburn and insomnia. These three symptoms were significantly different at each time point after baseline. Both dizziness and difficulty concentrating were higher in the herbal treatment group than the placebo group prior to treatment and these differences persisted at week 4 and month 3 for difficulty concentrating, but ceased to be different after week 4 for dizziness. Placebo subjects

Table 5 LOCF analysis of blood chemistries[a]

		Group				
		Placebo X ± s.d. (P-value)[b]		*Herbal X ± s.d. (P-value)*[b]		
Measure	*Study period*	*mmol/l*	*mg/dl*	*mmol/l*	*mg/dl*	P[c]
Total cholesterol	Baseline	5.34 ± 1.22	211 ± 48	5.11 ± 1.04	202 ± 41	0.203
	Final	5.27 ± 1.22	208 ± 48	4.94 ± 0.96	195 ± 38	0.082
	Change	− 0.07 ± 0.53	− 3 ± 21 (0.23)	− 0.17 ± 0.58	− 6 ± 23 (0.03)	0.404
LDL-cholesterol	Baseline	3.49 ± 1.06	138 ± 42	3.24 ± 0.86	128 ± 34	0.132
	Final	3.49 ± 1.06	138 ± 42	3.04 ± 0.84	120 ± 33	0.007
	Change	0 ± 0.43	0 ± 17 (0.84)	− 0.24 ± 0.51	− 8 ± 20 (0.0007)	0.013
HDL-cholesterol	Baseline	1.3 ± 0.4	52 ± 14	1.3 ± 0.4	51 ± 16	0.841
	Final	1.3 ± 0.3	51 ± 13	1.4 ± 0.4	54 ± 16	0.278
	Change	0 ± 0.18	0 ± 7 (0.73)	0.1 ± 0.2	3 ± 6 (0.0001)	0.004
Triglycerides	Baseline	2.93 ± 2.03	116 ± 80	3.11 ± 2.63	123 ± 104	0.650
	Final	2.73 ± 1.67	108 ± 66	2.78 ± 2.66	110 ± 105	0.890
	Change	− 0.20 ± 1.14	− 7 ± 48 (0.20)	− 0.33 ± 1.04	− 12 ± 41 (0.01)	0.515
Glucose	Baseline	5.0 ± 0.7	91 ± 12	5.0 ± 0.7	90 ± 12	0.592
	Final	5.2 ± 0.4	94 ± 16	4.9 ± 0.5	89 ± 9	0.056
	Change	0.2 ± 0.5	3 ± 9 (0.02)	− 0.1 ± 0.6	0 ± 10 (0.68)	0.051

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day.
[b]*P*-values for within group change from baseline compared by paired samples, two-sided *t*-tests.
[c]Mean values of subjects in treatment ($n = 70$) *vs* placebo ($n = 69$) groups compared by ANOVA analysis, followed by pairwise *t*-tests of baseline and final values and changes from baseline, with alpha set at 0.05.

Table 6 LOCF analysis of self-reported symptoms

	Symptom								
	Acute phase					*Chronic phase*			
	B	*W1*	*W2*	*W3*	*W4*	*B*	*M1*	*M3*	*M6*
Constipation	—	H > p**	H > P**	H > P**	—	—	—	—	—
Diarrhea	—	—	—	—	—	—	—	P > H*	P > H*
Difficulty concentrating	H > P*	—	—	—	H > P*	H > P*	—	H > P*	—
Dizziness	H > P*	H > P*	H > P*	—	H > P*	—	—	—	—
Dry mouth	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Heartburn	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P*
Insomnia	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Anxiety	—	H > P*	—	—	—	—	—	—	—
Upset stomach	—	H > P*	H > P*	—	—				

Acute phase: B, baseline (prior to treatment); W1, W2, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n = 69$) or placebo (P, $n = 68$).
Chronic phase: B, baseline (prior to treatment); M1, M3, M6, months 1, 3 and 6 after treatment with either herbal (H, $n = 66$) or placebo (P, $n = 70$).
*$P < 0.05$; **$P < 0.01$ (repeated measures ANOVA of group by time interaction, followed by pair-wise *t*-tests).
There were no differences between treatment groups at any time point for blurred vision, chest pain, headache, irritability, nausea or palpitations.

reported more diarrhea than herbal subjects at both 3 and 6 month time points. There were no significant differences between treatment groups in self-reported chest pain, palpitations, blurred vision, headache, nausea or irritability at any time point (not shown).

Adverse effects. Reasons for withdrawal from the study are presented in Table 7. The largest reason in each group was subject choice (P, 24; H, 14). This category included subjects who did not want to continue, moved away or had changes in jobs or personal lives that reduced available time. Investigators removed seven subjects from each group for protocol violations (previously undisclosed ineligibility or noncompliance). Fifteen subjects (eight P, seven H) were asked to withdraw from the study for potential adverse effects. These included one subject who had gallbladder surgery (P) and one with elevated serum creatinine (H). All other investigator-requested withdrawals were for cardiovascular symptoms: elevated blood pressure (three P, two H), irregular heartbeat (one P, one H), MFVE (one P, one H), ventricular events (one P, one H), and ventricular runs of five or more (one P, one H). Four additional subjects withdrew from each group for self-reported cardiovascular symptoms—chest pain (two P, none H), 'loud heart beat' (none P, one H) and palpitations (two P, three H). Subjects also voluntarily withdrew for self-reported CNS effects (two P, five H), and other GI effects (one P, four H). The numbers of subjects who withdrew from the study did not differ ($P > 0.05$) between treatment groups for any individual reason or for any of the system categories.

Table 7 Reasons for withdrawal from study by randomized subjects

	Number withdrawing		
Reason for withdrawal	*Placebo (n = 43, 51%)*	*Herbal (n = 37, 44%)*	*P-value* 0.44
Subject choice	24	14	0.12
Protocol violation	**4**	**4**	**1.0**
Noncompliance	**3**	**3**	**1.0**
Cardiovascular			
Chest pain	2	0	0.50
Loud heart beat	0	1	0.46
Palpitations	2	3	0.66
Elevated blood pressure	**3**	**2**	**1.0**
Irregular heart beat	**1**	**1**	**1.0**
Multifocal ventricular event	**1**	**1**	**1.0**
Ventricular event	**1**	**1**	**1.0**
Ventricular runs of five or more	**1**	**1**	**1.0**
Total	11	10	0.80
Central nervous system			
Anxiety	0	1	0.46
Disorientation	1	0	1.0
Dizziness	1	0	1.0
Insomnia	0	2	0.21
Irritability	0	2	0.21
Total	2	5	0.24
Gastrointestinal			
Bad taste	1	1	1.0
Dry mouth	0	1	0.46
Gastroesophogeal reflux disorder	0	1	0.46
Nausea	0	1	0.46
Gallbladder removal	**1**	**0**	**1.0**
Total	2	4	0.41
Other			
Elevated creatinine	**0**	**1**	**0.46**

Total number of subjects randomized: 84 to placebo, 83 to herbal supplement (90 mg/day ephedrine and 192 mg/day caffeine). Numbers do not sum to total *n*s due to multiple reasons for withdrawal by some subjects. Roman type indicates subject choice or subject self-reported reason for withdrawal. Bold type indicates choice for withdrawal was made by medical and/or research staff.

Discussion

In this study, a herbal preparation containing ephedra alkaloids (from Ma Huang) and caffeine (from Kola nut), administered with diet and exercise counseling for a 6 month period, promoted significantly greater reductions in body weight, body fat and waist and hip circumferences in overweight subjects compared with similarly counseled placebo-treated subjects. Other beneficial effects that accompanied the greater weight loss of the herbal treatment group included decreased serum LDL-cholesterol, increased HDL-cholesterol levels and decreased blood glucose. These beneficial responses observed in actively treated subjects were accompanied by small persistent increases in heart rate (4 ± 9 bpm by office visit and 1 ± 7 bpm by Holter monitor). Small increases in blood pressure (≥ 3 mmHg) were also detected by 24 h ambulatory blood pressure monitor, although not by office assessment. The numbers of subjects removed from the study for potential treatment-related adverse events were similar in the herbal and placebo groups. Self-reported symptoms that were increased in the herbal treatment group were dry mouth, heartburn and insomnia. There was no difference between groups in self-reporting of palpitations or chest pain at any time point.

Body composition-related effects

The increased weight reduction with the Ma Huang/Kola nut combination in the present study is consistent with results from two previous 8 week studies of Ma Huang formulations.[11,12] These results are also consistent with those from studies of synthetic ephedrine/caffeine combinations in animals[16,17] and humans.[6,9,18] Increased weight loss with ephedrine/caffeine combination is attributed to both decreased food intake[19,20] and increased energy expenditure.[17,20]

As in the two 8 week studies, the reductions in body fat, waist and hip circumferences and the favorable changes in serum HDL and LDL cholesterol levels are probable consequences of the greater reductions in body weight in the subjects treated with the Ma Huang/caffeine combinations. It has been suggested, however, that ephedrine/caffeine combinations have specific effects to increase lipolysis and improve blood lipid profile.[21,22]

The greater body weight loss seen in the herbal treatment group here was probably also responsible for the reduction in blood glucose levels in this group *vs* placebo subjects, although this difference was not seen in a previous 8 week study.[11] Several differences between the studies could account for this, including differences in the ephedra/caffeine ratio (70/240 *vs* 90/192 mg/day), in the herbal formulations and in study length (8 weeks *vs* 6 months). Another possibility is that subjects in the present study were more careful to refrain from taking their herbal supplements prior to blood sampling, thus avoiding influence of a possible acute increase in blood glucose in the group taking the ephedra/caffeine combination.[23]

Cardiovascular effects

The effect of herbal ephedrine/caffeine combinations on blood pressure appears to be small, with previous reports of either no increase[12] or small, transitory increases.[11] As discussed elsewhere,[11] these effects on blood pressure are less than those reported with sibutramine treatment.[24] In the present study, no significant change in blood pressure was detected by office evaluation. The only statistically significant increases that were revealed with 24 h monitoring were small (≤ 3 mmHg) and some blood pressure measures were found to be significantly decreased (≤ 5 mmHg). Similar acute[19] and transitory[9] increases in blood pressure have been previously described with synthetic ephedrine/caffeine treatment.

The small increases in heart rate of herbally treated subjects in this study are similar in magnitude (4 ± 9 bpm) to those observed in the previous 8 week study[11] and to those reported following acute treatment with Ma Huang,[25] or with ephedrine/caffeine.[20] Increased heart rate is consistent with the known effect of this combination to stimulate energy expenditure.[20,26] Chronic treatments with ephedrine/caffeine have been reported to have either no significant effect on heart rate[9] or a slower rate of decrease subsequent to weight loss than seen in placebo-treated subjects.[23]

Despite the small statistically significant increases in heart rate observed in this study, there were no significant increases subsequent to herbal treatment in any of the cardiac arrhythmias assessed. The decrease in incidents of bradycardia with ephedra/caffeine is related to the demonstrated effect of this combination to increase heart rate. Although there has been speculation of a link between consumption of low levels of ephedra alkaloids and arrhythmias,[2] the finding of no cause and effect relationship in the present placebo-controlled study is consistent with the lack of any research data linking synthetic ephedrine to cardiac arrhythmias.[27]

Adverse effects

There were no significant adverse effects resulting from treatment with herbal ephedra/caffeine in the present study. Some subjects were asked to withdraw and some withdrew themselves from this double-blind study for potential treatment-related side effects. Analysis upon completion of the study, however, revealed that the distribution of these subjects was almost identical between the treatment and placebo groups.

How can the absence of treatment-related adverse events in this and two previous clinical trials of ephedra combinations (334 subjects in total) be reconciled with the adverse event reports collected by the FDA from users of these products? Possible explanations include coincidence, pre-existing pathology, non-recommended usage and increased individual sensitivity.

In a FDA-sponsored analysis, Haller and Benowitz categorized 140 adverse-event reports based on how likely they believed the reported events to have resulted from the use of ephedra supplements.[2] The difficulty in making such judgements is illustrated by the controversy regarding their conclusions.[28,29] With millions of Americans consuming ephedra-containing products, it is obvious that some number of adverse events is expected each year regardless of consumption of these products. The real question is not whether adverse events occur in a population undergoing treatment, but whether these occur at a rate that is higher than that of a matched, untreated group. This is impossible to determine from adverse event reports alone. The randomized, placebo-controlled trial allows evaluation of cause and effect relationships *vs* coincidental events.

Most clinical trials purposely exclude individuals with pre-existing medical conditions to avoid confounding of results. It is therefore not justified to extrapolate results from such trials to individuals with such exclusionary medical conditions or to extrapolate results beyond amounts or time periods that have been studied. The possibility of unfavorable interactions between herbal combinations and other medications, either prescription or illicit, should be recognized and warning labels present on herbal products should be adhered to.

Some have expressed the theory that adverse event reports may reflect an unusually high degree of sensitivity in a small fraction of individuals.[2,25] Because of the low suspected incidence, this type of sensitivity might not be revealed in a clinical trial, but requires a case–control study of a very large number of individuals.[25] Such a study would be difficult to conduct, but may be the only way to address the question of rare hypersensitivity.

Conclusion

The present study demonstrated significant beneficial effects on body weight, body fat and blood lipids of a herbal Ma Huang/Kola nut mixture (90/192 mg/day ephedrine alkaloids/caffeine) in overweight men and women who were otherwise healthy. Compared with placebo, the tested product produced no adverse events and minimal side effects that are consistent with the known mechanisms of action of

ephedrine and caffeine. Extrapolation of the present findings to usage by individuals with medical complications (diabetes, heart disease, etc) is unwarranted and usage by such individuals is contra-indicated on labels of commercial products. Evidence from three completed placebo-controlled clinical trials of herbal ephedra/caffeine is consistent with that from a large number of studies with synthetic ephedrine/caffeine. In total, these suggest that herbal ephedra/caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events. The current widespread usage of herbal products and the increasing incidence of obesity warrant additional clinical trials to confirm and extend these results.

Acknowledgements

The authors gratefully acknowledge the help of the following individuals: Wayne Snodgrass, MD, PhD, for contributing to protocol design; Stanley Heshka, PhD, for the randomization procedure; Sheila Dawling, PhD, for supervising urine toxicologic screening, Steven B Heymsfield, MD, for EKG evaluations and for supervision of physical evaluations. Research support was provided by: Science Toxicology and Technology Consulting, San Francisco, CA, USA and National Institutes of Health grant P30DK 26687.

References

1 NBC Nightly News. In Depth Report, 10 April, 2001.
2 Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *New Engl J Med* 2000; **343**: 1833 – 1838.
3 Food and Drug Administration. *Fed Reg* 1997; **62**: 30678 – 30724.
4 Neergaard L. Since recent deaths, the FDA is studying dangers of ephedra. *Associated Press* 17 April, 2000.
5 Spake A. Natural hazards. *US News World Rep* 12 February, 2001, pp 42 – 49.
6 Malchow-Moller A, Larsen S, Hey H, Stokholm KH, Juhl E, Quaade F. Ephedrine as an anorectic: the story of the 'Elsinore pill'. *Int J Obes* 1981; **5**: 183 – 187.
7 Toubro S, Astrup AV, Breum L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. *Int J Obes Relat Metab Disord* 1993; **17**(Suppl 1): S69 – S72.
8 Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. *Int J Obes Relat Metab Disord* 1992; **16**: 269 – 277.
9 Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L. Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity. *Int J Obes Relat Metab Disord* 1993; **17**(Suppl 1): S73 – S78.
10 Breum L, Pedersen JK, Ahlstrom F, Frimodt-Moller J. Comparison of an ephedrine/caffeine combination and dexfenfluramine in the treatment of obesity. A double-blind multi-centre trial in general practice. *Int J Obes Relat Metab Disord* 1994; **18**: 99 – 103.
11 Boozer C, Nasser J, Heymsfield S, Wang V, Chen G, Solomon J. An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord* 2001; **25**: 316 – 324.
12 Kaats G, Adelman J, Blum K. Effects of a multiple herbal formulation on body composition, blood chemistry, vital signs, and self-reported energy levels & appetite control. *Int J Obes Relat Metab Disord* 1994; **18**: S145.
13 Lohman T. *Advances in body composition assessment*. Human Kinetics: Champaigne, IL; 1992.
14 Siri W. Body composition from fluid spaces and density: analysis of methods. In: *Techniques for measuring body composition*. NAS: Washington, DC; 1961. pp 223 – 248.
15 Agresti A. *Categorical Data Analysis*. Wiley: New York, 1990.
16 Dulloo AG, Miller DS. Reversal of obesity in the genetically obese *fa/fa* Zucker rat with an ephedrine/methylxanthines thermogenic mixture. *J Nutr* 1987; **117**: 383 – 389.
17 Dulloo AG, Miller DS. The thermogenic properties of ephedrine/methylxanthine mixtures: animal studies. *Am J Clin Nutr* 1986; **43**: 388 – 394.
18 Toubro S, Astrup A, Breum L, Quaade F. The acute and chronic effects of ephedrine/caffeine mixtures on energy expenditure and glucose metabolism in humans. *Int J Obes Relat Metab Disord* 1993; **17**(Suppl 3): S73 – S77.
19 Dulloo AG, Miller DS. Aspirin as a promoter of ephedrine-induced thermogenesis: potential use in the treatment of obesity. *Am J Clin Nutr* 1987; **45**: 564 – 569.
20 Astrup A, Toubro S, Cannon S, Hein P, Madsen J. Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study. *Metabolism* 1991; **40**: 323 – 329.
21 Astrup A, Buemann B, Christensen NJ *et al*. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. *Metabolism* 1992; **41**: 686 – 688.
22 Buemann B, Marckmann P, Christensen NJ, Astrup A. The effect of ephedrine plus caffeine on plasma lipids and lipoproteins during a 4.2 MJ/day diet. *Int J Obes Relat Metab Disord* 1994; **18**: 329 – 332.
23 Astrup A, Toubro S. Thermogenic, metabolic, and cardiovascular responses to ephedrine and caffeine in man. *Int J Obes Relat Metab Disord* 1993; **17**(Suppl 1): S41 – S43.
24 Bray GA, Blackburn GL, Ferguson JM, Greenway FL, Jain AK, Mendel CM, Mendels J, Ryan DH, Schwartz SL, Scheinbauml ML, Seaton TB. Sibutramine produces dose-related weight loss. *Obes Res* 1999; **7**: 189 – 198.
25 White LM, Gardner SF, Gurley BJ, Marx MA, Wang PL, Estes M. Pharmacokinetics and cardiovascular effects of ma-huang (*Ephedra sinica*) in normotensive adults. *J Clin Pharmac* 1997; **37**: 116 – 122.
26 Ramsey JJ, Colman RJ, Swick AG, Kemnitz JW. Energy expenditure, body composition, and glucose metabolism in lean and obese rhesus monkeys treated with ephedrine and caffeine. *Am J Clin Nutr* 1998; **68**: 42 – 51.
27 Karch S. Ma Huang and the ephedra alkaloids. In: Cupp M (ed.), *Toxicology and clinical pharmacology of herbal products*. Humana Press: Totowa, NJ; 2000. pp 11 – 30.
28 Fleming GA. The FDA, regulation, and the risk of stroke. *New Engl J Med* 2000; **343**, 1886 – 1887.
29 Hutchins GM. Dietary supplements containing ephedra alkaloids. *New Engl J Med* 2001; **344**: 1095 – 1096.

Appendix I: medical exclusions from the study

Active heart disease, a positive history of palpitations, hypertension (office measurement ≥ 140 systolic BP or diastolic BP ≥ 90 or ABPM mean 24 h systolic BP ≥ 139 mmHg or diastolic BP ≥ 87 mmHg), epilepsy, history of mental illness, hyperthyroidism, chronic use of any drug (by self-report or by presence in urine toxicology screen) except oral contraceptives, hormone replacement therapy or synthetic thyroid hormone, active bulimia, known prostatic hypertrophy, pregnancy (reported or detected by HCG testing), glaucoma, active cancer or cancer in remission for ≤ 5 y, renal dysfunction, liver dysfunction (ALT, alkaline phosphatase $> 2\times$upper limit of normal), acute or chronic active hepatitis, AIDS, any acute illness within the past 4 weeks, any other chronic illness that might be adversely impacted by concurrent use of the herbal compound, concurrent participation in another research protocol involving diet or any drug use, concurrent participation in a diet program involving severe calorie restriction (800 or fewer calories per day), caffeine intake of 500 mg per day or greater, use of appetite suppressant drugs or ephedra-containing herbal supplements within the last 6 months and weight change of 5 kg or more within the past 3 months.

Appendix II: urine toxicology screen

Amphetamine metabolites, salicylates, phenothiazines, amphetamine class, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, tricyclics, methanol, ethanol, acetone, iso-propanol, ethchlorvynol.