

Effect of a Dietary Herbal Supplement Containing Caffeine and Ephedra on Weight, Metabolic Rate, and Body Composition*

Frank L. Greenway, Lilian de Jonge, Damian Blanchard, Madlyn Frisard, and Steven R. Smith

Abstract

GREENWAY, FRANK L., LILIAN DE JONGE, DAMIAN BLANCHARD, MADLYN FRISARD, AND STEVEN R. SMITH. Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. *Obes Res.* 2004;12:1152–1157.

Objective: To evaluate the effect of a dietary supplement containing herbal caffeine (70 mg/dose) and ephedra (24 mg/dose; C&E) on metabolic rate, weight loss, body composition, and safety parameters.

Research Methods and Procedures: In phase I, 12 healthy subjects with a BMI of 25 to 35 kg/m² had resting metabolic rate (RMR) measured for 2 hours after ingesting C&E or a placebo on two occasions 1 week apart, followed by a 1-week washout before phase II. In phase II, these 12 and 28 additional subjects were randomized to a 12-week, double-blind trial comparing C&E (3 times/day) to placebo. In phase III, the C&E group was given open-label C&E for 3 months, and the placebo group was given C&E for 6 months.

Results: In phase I, C&E gave an average $8 \pm 0.1\%$ (SE) rise in RMR over 2 hours compared with placebo ($p < 0.01$). In phase II, weight loss at 12 weeks was 3.5 ± 0.6 kg with C&E compared with 0.8 ± 0.5 kg with placebo ($p < 0.02$). The percentage fat lost, shown by DXA, was $7.9 \pm 2.9\%$ with C&E and $1.9 \pm 1.1\%$ with placebo ($p < 0.05$). Pulse decreased more in the placebo group than in the C&E group ($p < 0.03$). There were no differences in lipid levels

or blood pressure. In phase III, there was a 6-month loss of 7.3% and 7.8% of initial body weight for the groups on placebo and C&E during phase II, respectively. There were no serious adverse events.

Discussion: C&E increased RMR significantly by 8% compared with placebo, promoted more weight and fat loss than placebo, and was well tolerated.

Key words: ephedra, caffeine, metabolic rate, body composition, herbal dietary supplement

Introduction

Since the enactment of the Dietary Supplement Health and Education Act in 1994, dietary herbal supplements have been regulated as foods with the presumption of safety. In the last decade, the sale of herbal dietary supplements in the United States has increased dramatically. Caffeine and ephedra (C&E)¹ from herbal sources are classified as dietary herbal supplements and have become popular in weight loss products. In fact, an estimated three billion doses of ephedra-containing supplements were sold in 1999 (1). The unregulated sale of ephedra-containing supplements, however, has become controversial because of reports of adverse events (2).

Caffeine and theophylline are xanthines that have the same mechanism of action; 1 mg of theophylline is equivalent to 2 mg of caffeine (3). Caffeine or theophylline combined with ephedrine has a long history of use in prescription medications to treat asthma. In fact, caffeine/theophylline and ephedrine were the standard treatment for asthma in adults and children in the United States until more specific β -adrenergic stimulators were introduced in the 1970s (4). During the early 1970s, involuntary weight loss was observed in subjects being treated with C&E for asthma

*Ephedra is no longer a dietary herbal supplement due to an FDA ruling made in February 2004 in which ephedra was declared to present an unreasonable risk of illness or injury.

Received for review August 21, 2003.

Accepted in final form May 18, 2004.

The costs of publication of this article were defrayed, in part, by the payment of page charges. This article must, therefore, be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Pennington Biomedical Research Center, Baton Rouge, Louisiana 70808.

Address correspondence to Frank L. Greenway, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808-4124.

E-mail: greenwfl@pbrc.edu

Copyright © 2004 NAASO

¹ Nonstandard abbreviations: C&E, caffeine and ephedra; FDA, Food and Drug Administration; LDL, low-density lipoprotein; HDL, high-density lipoprotein; RMR, resting metabolic rate; EGCG, epigallocatechin gallate.

in Denmark (5). Until recently, a prescription medication containing C&E was marketed for weight loss in Denmark, and the trials leading to its approval have been used by manufacturers of herbal caffeine and ephedra to support the safety of their weight loss products (6).

Few trials of herbal caffeine and ephedra have been published, possibly because, unlike prescription medication, the presumption of safety does not require clinical testing before marketing (7,8). Ephedra contains four isomers, of which ephedrine is the most active, and this has been the basis on which ephedra has been compared with the prescription ephedrine products (9). There are at least two differences between prescription C&E products and the dietary herbal supplements containing C&E that make that comparison difficult.

The first is a lack of regulations requiring standardization and quality control of herbal products. This causes the active ingredients in some herbal products to vary from batch to batch, a situation that the Food and Drug Administration (FDA) is in the process of addressing. The second is the addition of other herbs to the C&E mixture, a practice that most manufacturers use to give their products brand identity. These additional herbs have the potential to cause adverse events or adverse herb interactions. Therefore, not only is there a need for further trials to test the safety and efficacy of herbal caffeine- and ephedra-containing products in general, but it is also desirable to test the safety and efficacy of the various formulations sold.

C&E products are sold to increase metabolism and to cause weight loss. This trial tested a commercial caffeine- and ephedra-containing product in three phases. The first phase tested the efficacy of the product in raising metabolic rate compared with a placebo. The second phase was a double-blind, placebo-controlled randomized 12-week trial testing the safety and efficacy of the herbal caffeine- and ephedra-containing product. The third phase was a 3- or 6-month open-label treatment to observe the safety and weight loss over 6 months in all participants.

Research Methods and Procedures

Phase I

Twelve healthy male and female subjects between 18 and 65 years of age, with a BMI between 25 and 35 kg/m², were enrolled in this phase of the study. Subjects who were pregnant, nursing, smokers, or taking regular medication except birth control pills or hormone replacement therapy were excluded from the study. Subjects taking monoamine oxidase inhibitor medications, methyl dopa, drugs for Parkinson's disease, or products containing ephedrine alkaloids were specifically excluded. Subjects with known thyroid disease, diabetes, blood pressure >140/90 mm Hg, depression, psychiatric disorders, glaucoma, prostatism, or seizure disorders were also excluded. During screening, all subjects

underwent a medical history, physical examination, electrocardiogram, blood tests [glucose, creatinine, potassium, uric acid, albumin, calcium, magnesium, creatine phosphokinase, alanine leucine transpeptidase, alkaline phosphatase, thyroid-stimulating hormone, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, hemoglobin, hematocrit, mean cell volume, platelet count, white blood cell count, granulocyte number, neutrophil number, eosinophil number, and basophil number], and urinalysis (glucose, ketones, specific gravity, blood, and protein).

Subjects reported to the energy expenditure laboratory on 2 separate days, having fasted for 12 hours, refrained from strenuous physical activity for 24 hours, and eaten their usual diet in the 3 days before the test. On each visit, the subject rested for 30 minutes, after which resting metabolic rate (RMR) was measured for 30 minutes using a Deltatrac flow-through metabolic hood system (Deltatrac II; Datex-Ohmeda, Helsinki, Finland). The subjects were given two pills to swallow, after which their RMR was measured for 30 minutes of each hour for 2 hours. On one occasion, each pill was an herbal product containing 150 mg ma huang concentrate 8% (arial; 12 mg ephedra), 150 mg kola nut (seed) 20% caffeine (30 mg caffeine), 50 mg green tea (10% caffeine, 20% polyphenols; 5 mg caffeine), 50 mg L-phenylalanine, 50 mg ginger root, 50 mg fo-ti root, 50 mg lycii berry fruit, 50 mg Siberian ginseng root, 50 mg cinnamon bark, 100 mg chromium (arginate), 5 mg zinc (aspartate), 50 mg vanadium (aspartate), 20 mg magnesium (aspartate), 50 mg adrenal gland, 30 mg astragalus (root), 20 mg ginkgo biloba 24/6, and 10 mg pyridoxal α -ketoglutarate per pill (FormuLean, Denver, CO). On the other occasion, each pill was a placebo. The order was balanced, the assignment was made randomly, and the study was double-blinded.

Subjects participating in any phase of this trial deposited \$100 of their own money and received a credit of \$10 for each of the 10 clinic visits they attended. The credits were refunded to them on completion of the study. Subjects who dropped from the study for adverse events had their entire deposit returned. Subjects who completed the study received a 3-month supply of the herbal caffeine and ephedrine product for their personal use in addition to earning back the credits on their deposit.

The difference in the area under the curves above baseline for energy expenditure during the 2 hours after taking placebo or the dietary supplement containing herbal caffeine and ephedrine was compared. The results were analyzed using the Student's *t* test for paired samples, with the subjects serving as their own controls.

Phase II

The 12 subjects that participated in phase I plus 28 additional subjects, who were screened using the same inclusion-exclusion criteria as described in phase I, partic-

ipated in phase II. These 40 subjects were randomly assigned to the herbal product described in detail above containing C&E (20 subjects) or placebo (20 subjects) in a double-blind fashion. All subjects were seen monthly for 3 months, and the 20 C&E subjects were asked to take two pills (together containing 70 mg herbal caffeine and 24 mg herbal ephedrine) three times per day with meals. Blood pressure, weight, pulse rate, and any adverse events were recorded during the monthly visits, and medication was collected and dispensed. Subjects were seen in the morning fasting at baseline and at 3 and 6 months. On these visits, the last pill of study medication was taken the prior afternoon. On the other visits, subjects took their study medications within 4 hours of the visit. Total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and body composition by DXA (QDR-4500; Hologic, Waltham, MA) were assessed at the beginning and end of this 3-month period.

At the beginning of phase II, all subjects were seen by a registered dietitian and instructed in a balanced 1200 kcal/d diet as recommended by the American Diabetes Association for women and a 1500 kcal/d diet as recommended by the American Diabetes Association for men. The subjects were given written information describing the diet and were asked to follow it during the remaining phases of the study. Subjects were asked to take two pills three times per day with their meals. They were also asked to walk 5 minutes three times per day and gradually increase their walking to 10 minutes four times per day or 40 minutes/d. All subjects were given written information on lifestyle changes to incorporate into their daily lives during the study, including such things as setting their fork down between bites, putting food into opaque containers for storage, and putting their food on smaller plates. Compliance was evaluated by pill counts of the bottles returned on each visit. The weight, pulse, and blood pressure in phase II were compared using the mixed model with repeated measures analysis (SAS Institute, Cary, NC). The body composition by DXA and lipids were compared using the Student's *t* test. Adverse events, demographic data, and dropouts were compared by χ^2 test.

Phase III

At the end of the 3-month double-blind period, all subjects were placed on the dietary herbal supplement and took two capsules three times per day. The subjects who were randomized to the dietary herbal supplement in phase II remained in phase III for 3 months. The subjects who were randomized to placebo during phase II were continued in phase III for 6 months. Subjects were seen monthly during phase III. Blood pressure, weight, pulse rate, and any adverse effects were recorded during the monthly visits, and medication was collected and dispensed. At the end of phase III, the physical exam, blood tests except thyroid-stimulat-

Table 1. Baseline characteristics of subjects in the herbal caffeine and placebo groups

Variable	C&E	Placebo	<i>p</i>
No. enrolled	20	20	
Gender			NS
Female	16	17	
Male	4	3	
Race			NS
Black	6	4	
White	14	16	
Age (years)	46.8 ± 2.8	45.3 ± 1.9	NS
BMI (kg/m ²)	29.7 ± 0.5	29.6 ± 0.5	NS
Weight (kg)	82.8 ± 3.2	83.2 ± 2.0	NS

The groups were well matched for age, gender, race, and weight. Values are means ± SD. NS, not significant.

ing hormone, electrocardiogram, and urinalysis were repeated. Results of phase III were descriptive because of the absence of a control group. Subjects who completed phase III were given a gift of an additional 3-month supply of the herbal dietary supplement product for home use.

Results

Phase I

All 12 patients completed phase I of the study. The RMR was $8 \pm 0.1\%$ (SE) higher when the subjects took the dietary herbal supplement containing C&E than when they took the placebo ($p < 0.01$).

Phase II

Baseline characteristics of the 40 subjects enrolled in the two groups in this study were well matched and are described in Table 1. Thirty-one subjects completed the study, 12 in the group taking the dietary herbal supplement containing C&E and 19 in the placebo group. There was one withdrawal in the placebo group for a scheduling conflict. There were eight withdrawals in the C&E group: five were lost to follow-up, two withdrew consent, and one dropped out for an adverse event (breast tenderness). The adverse events are listed in Table 2. The study took place in the spring. Pollen allergy symptoms were common in both groups, but there was no statistically significant difference in the incidence of adverse events between the two groups. The adrenergic symptoms typically associated with caffeine or ephedra were not seen in excess of the placebo group. The reason for this is not clear, but it is possible that the five patients lost to follow-up in the C&E group may have failed to return because of adrenergic symptoms. There were no

Table 2. Number of subjects reporting adverse events during phase II

Group	C&E	Placebo	<i>p</i>
Respiratory	11	8	NS
Pain	1	3	NS
Gastrointestinal	2	5	NS
Oral	1	4	NS
Genitourinary	0	3	NS
Headache	2	1	NS
Pinched nerve	0	1	NS
Hair loss	1	0	NS
Skin problem	1	0	NS
Neuropsychiatric	1	1	NS
Arrhythmia	0	1	NS

The adverse events seen in the double-blind portion of this trial are listed as the actual numbers of adverse events for subjects in each group. The study was conducted in the spring of the year, and respiratory complaints were common in both groups. There were no serious adverse events, and there was one dropout as a result of an adverse event (breast tenderness in the herbal C&E group). NS, not significant.

serious adverse events in the study, and the only arrhythmia was seen in the placebo group.

The weight loss in the C&E group was 3.5 ± 0.5 kg compared with 0.8 ± 0.5 kg in the placebo group. This difference was significant as a treatment effect ($p < 0.02$), a time effect ($p < 0.001$), and a time \times treatment interaction ($p < 0.001$). Percent weight loss is shown in Figure 1. Compliance during phase II, measured by pill count, averaged 90%, and there was no difference between groups.

Pulse rate decreased 0.3 bpm below baseline in the C&E group compared with a 6.6 bpm decrease in the placebo group. This difference was significant as a treatment effect ($p < 0.03$) and a time effect ($p < 0.04$), but not as a time \times treatment interaction. The slice effects of the time \times treatment interaction were significant for pulse differences at 1 ($p < 0.04$) and 3 months ($p < 0.04$). While systolic and diastolic blood pressure dropped 4/1 mm Hg below baseline at 3 months in the C&E group, there was no significant difference in blood pressure between the C&E and placebo groups ($p > 0.1$).

There was no significant difference between the C&E group and the placebo group in total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides at 3 months.

Percent weight loss at 3 months by DXA was $4.8 \pm 1.5\%$ in the C&E group compared with $0.9 \pm 0.8\%$ in the placebo group ($p < 0.02$). The percentage fat loss at 3 months, measured by DXA, was $7.9 \pm 2.9\%$ in the C&E group

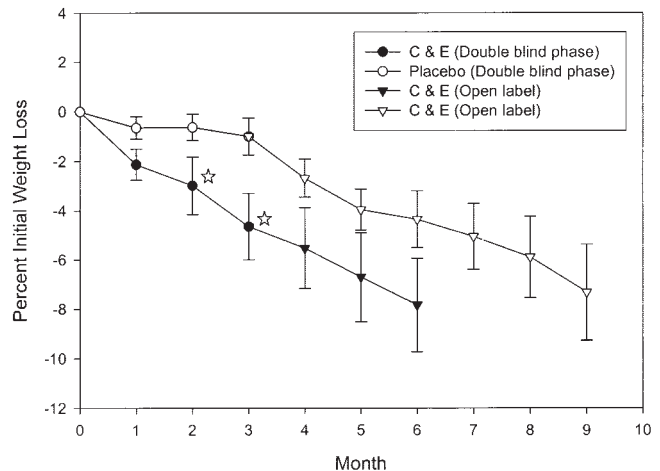


Figure 1: The first 3 months are the double-blind period. Twelve of 20 subjects in the C&E group and 19 of 20 in the placebo group completed this portion of the study. The C&E group lost $4.3 \pm 0.7\%$ of initial body weight compared with $1.0 \pm 0.6\%$ in the placebo group at the end of 3 months. This difference was significant by treatment effect ($p < 0.02$), by time effect ($p < 0.0001$), and by time \times treatment interaction ($p < 0.01$). The time slices showed significant differences (\star) at 2 months ($p < 0.01$) and 3 months ($p < 0.005$). At the end of 6 months of treatment with C&E, the group originally on C&E lost $7.8 \pm 1.9\%$ of their initial body weight, and the group originally on placebo lost $7.3 \pm 1.9\%$.

compared with $1.9 \pm 1.1\%$ in the placebo group ($p < 0.05$). The percentage loss of lean tissue was $1.7 \pm 1.1\%$ in the C&E group compared with $0.27 \pm 0.9\%$ in the placebo group, a nonsignificant difference. The C&E group lost less lean tissue as a percentage of total weight loss compared with the placebo group, but this difference did not reach statistical significance ($p > 0.2$).

Phase III

Eleven of the 12 subjects in the group originally randomized to C&E completed phase III, and the subject who dropped out withdrew consent for reasons unrelated to an adverse event. Thirteen of the 19 subjects in the group originally randomized to placebo completed phase III; 1 withdrew consent for reasons unrelated to an adverse event, 3 were lost to follow-up, and 2 withdrew because of an adverse event (1 for a slow urinary stream and 1 for insomnia, irritability, and poor-quality erections). The group that started on the herbal dietary supplement containing C&E lost $7.8 \pm 1.9\%$ of their body weight at 6 months. The group that started on placebo lost $7.3 \pm 1.9\%$ of their body weight after 6 months of treatment with C&E. Weight loss is shown in Figure 1. The weight loss during the open-label period followed the typical weight loss curve, in which the 6-month weight loss on drug was approximately double the weight loss at 2 months on the drug. It was anticipated that

weight loss would plateau at 6 months, based on prior studies with C&E. Including the open-label phase in the trial allowed all patients to have active treatment during the trial and allowed for the anticipated weight loss plateau at 6 months of treatment to be observed. There were no serious adverse events and no evidence of toxicity on physical examination, urinalysis, or blood testing at the end of 6 months of treatment.

Discussion

This study attempted to evaluate the effect of a commercial herbal caffeine and ephedra product on energy expenditure, body weight, and safety when used as an adjunct to a weight loss program. Phase I showed an 8% mean increase in RMR compared with placebo. It has been shown in a previous study that mean increase of RMR using 20 mg ephedrine with 200 mg caffeine is 7% (10). Therefore, this study confirms, with an herbal dietary supplement, prior work with pharmaceutical grade C&E.

Phase II demonstrated the efficacy of C&E to induce significant weight loss compared with placebo. A power analysis based on a prior weight loss study done at our institution predicted that we could detect a 2-kg difference in weight between the two groups with 83% power, assuming an SD of 2 kg at an α of 0.05, if 12 subjects/group finished the study. Although the study by Astrup et al. (6) with pharmaceutical C&E showed greater weight loss, the placebo group lost more weight as well. This difference suggests a more vigorous diet and behavioral program superimposed on the C&E intervention than was used in this study. In this study, the placebo group lost 1% body weight, suggesting that the difference seen was almost totally attributable to the intervention with the dietary herbal supplement containing C&E.

This product contained not only C&E, but also green tea catechins and other presumably inactive herbs. Green tea catechins contain epigallocatechin gallate (EGCG), an inhibitor of catechol-*o*-methyl transferase, the enzyme that breaks down norepinephrine. Dulloo et al. (11,12) have shown that EGCG is synergistic with C&E in raising energy expenditure, but the amount of EGCG in combination with caffeine needed to raise metabolic rate by 4% is 180 mg/d. Therefore, it is unlikely that the 30 mg/d of green tea catechin used for this study, only part of which would have been EGCG, had a clinically significant effect on energy expenditure or weight loss in this trial.

The herbs other than C&E contained in the supplement are unlikely to have added to its therapeutic effect. Phenylalanine suppresses food intake at doses >10 g/d (13), but the supplement contains only 1% of the effective amount. Phenylalanine combined with other herbs has been shown in a clinical trial not to promote weight loss (14). Ginseng has been shown not to affect metabolism during $\dot{V}O_{2\max}$ testing (15). Chromium has been shown not to affect body compo-

sition or metabolic rate (16). Zinc deficiency is associated with stunting in children (17) and decreased taste (18), so supplementation would not be expected to help in weight loss. Magnesium, in larger amounts than contained in the supplement and mixed with potassium, increases postprandial thermogenesis (19), but does not increase oxygen uptake with exercise (20). Thus, there is no evidence that the herbs other than C&E in the dietary herbal supplement tested significantly affected weight, appetite, or metabolic rate.

The results of the DXA scans not only confirm the loss of body weight but also document the loss of body fat. Although there was a suggestion that weight loss with the dietary herbal supplement containing C&E preserved lean tissue, this did not reach statistical significance. Preservation of lean tissue with C&E has been documented to occur with a pharmaceutical product containing C&E (6).

There was no difference in the fall of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides at 3 months between the C&E and placebo groups. The lack of difference of lipid levels between the C&E group and placebo group at 3 months may be because of the continuing weight loss. At the end of 6 months of treatment with the dietary herbal supplement containing C&E, total cholesterol, LDL-cholesterol, and triglycerides decreased, whereas HDL-cholesterol increased. Although there was no control group at 6 months, the findings are consistent with those in the 6-month study by Boozer et al. (7).

Although this trial, with its small number of subjects, did not have the power to detect rare adverse events, there were no serious adverse events noted. The only adverse event in this trial that could logically be attributed to catecholamines, arrhythmia, was seen in the placebo group. The lack of toxicity in this trial is consistent with other trials of C&E in both herbal and pharmaceutical forms (4,21) Phase III gives further evidence of safety. There was no evidence from physical examination, electrocardiogram, blood tests, or urinalysis of toxicity from a 6-month course of treatment with the herbal dietary supplement containing C&E.

Obesity is increasing in prevalence despite public health initiatives that encourage an increase in physical activity and other lifestyle changes to maintain a healthy weight (22). Lifestyle modification is clearly necessary to combat the obesity epidemic, but alone it is insufficient, to which the rising prevalence figures convincingly attest. Obesity is also an independent risk factor for diabetes and cardiovascular disease.

A 5% to 10% weight loss has been declared by the United States National Institute of Health–National Heart, Lung, and Blood Institute to be medically significant (23). This study shows a 7.3% to 7.8% weight loss with a dietary herbal supplement containing C&E. Although there are several groups that may be medically at risk for adverse events from taking C&E, most package labels warn these

individuals to seek medical advice before use. Based on this study and the other controlled studies with both herbal and pharmaceutical C&E, the benefits of weight loss seem to outweigh the risks associated with their use when used according to the labeling instructions.

Although, on the basis of the foregoing, we concluded that dietary herbal supplements containing C&E should remain available to obese individuals trying to control their weight, the FDA has removed ephedra as a dietary herbal supplement through a ruling issued in February 2004, making ephedra an adulterant. This action was apparently because of reports of adverse events associated with ephedra use. Some of these adverse event reports were associated with ephedra use to enhance athletic performance, a use for which only single dose trials have been done and a use for which no risk-to-benefit advantage exists. Because ephedra has been removed from the herbal dietary supplement market, any future use of C&E for weight loss will be off-label use under medical supervision by physicians prescribing these drugs.

Acknowledgments

This study was supported by grants from Science Technology and Toxicology (San Francisco, CA). We thank Mary Beth Burnett for manuscript preparation.

References

1. **FDC.** Dietary supplement market view. In: *FDC Reports*. Chevy Chase, MD: Elsevier, 2000.
2. **Haller CA, Benowitz NL.** Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833–8.
3. **Goodman L, Gilman A.** *The Pharmacological Basis of Therapeutics*. 7th ed. New York: Macmillan Publishing Company; 1985, p. 595.
4. **Greenway FL.** The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obes Rev*. 2001;2:199–211.
5. **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 Relat Metab Disord*. 1981;5:183–7.
6. **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;16:269–77.
7. **Boozer CN, Daly PA, Homel P, et al.** Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes Relat Metab Disord*. 2002;26:593–604.
8. **Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL.** An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord*. 2001;25:316–24.
9. **Vansal SS, Feller DR.** Direct effects of ephedrine isomers on human beta-adrenergic receptor subtypes. *Biochem Pharmacol*. 1999;58:807–10.
10. **Liu YL, Toubro S, Astrup A, Stock MJ.** Contribution of beta 3-adrenoceptor activation to ephedrine-induced thermogenesis in humans. *Int J Obes Relat Metab Disord*. 1995;19:678–85.
11. **Dulloo AG, Duret C, Rohrer D, et al.** Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr*. 1999;70:1040–5.
12. **Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J.** Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. *Int J Obes Relat Metab Disord*. 2000;24:252–8.
13. **Rogers PJ, Blundell JE.** Reanalysis of the effects of phenylalanine, alanine, and aspartame on food intake in human subjects. *Physiol Behav*. 1994;56:247–50.
14. **Hoeger WW, Harris C, Long EM, Hopkins DR.** Four-week supplementation with a natural dietary compound produces favorable changes in body composition. *Adv Ther*. 1998;15:305–14.
15. **Dowling EA, Redondo DR, Branch JD, Jones S, McNabb G, Williams MH.** Effect of *Eleutherococcus senticosus* on submaximal and maximal exercise performance. *Med Sci Sports Exerc*. 1996;28:482–9.
16. **Volpe SL, Huang HW, Larpadisorn K, Lesser II.** Effect of chromium supplementation and exercise on body composition, resting metabolic rate and selected biochemical parameters in moderately obese women following an exercise program. *J Am Coll Nutr*. 2001;20:293–306.
17. **Umata M, West CE, Haidar J, Deurenberg P, Hautvast JG.** Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. *Lancet*. 2000;355:2021–6.
18. **Schechter PJ, Prakash NJ.** Failure of oral L-histidine to influence appetite or affect zinc metabolism in man: a double-blind study. *Am J Clin Nutr*. 1979;32:1011–4.
19. **Jaedig S, Lindgarde F, Arborelius M.** Increased postprandial energy expenditure in obese women after peroral K- and Mg-phosphate. *Miner Electrolyte Metab*. 1994;20:147–52.
20. **Hagan RD, Upton SJ, Duncan JJ, Cummings JM, Gettman LR.** Absence of effect of potassium-magnesium aspartate on physiologic responses to prolonged work in aerobically trained men. *Int J Sports Med*. 1982;3:177–81.
21. **Shekelle PG, Hardy ML, Morton SC, et al.** Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA*. 2003;289:1537–45.
22. **Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL.** Overweight and obesity in the United States: prevalence and trends, 1960–1994. *Int J Obes Relat Metab Disord*. 1998;22:39–47.
23. **National Institutes of Health—National Heart, Lung, and Blood Institute.** Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res*. 1998;6:51S–210S.