Efficacy and Tolerance of an Ephedra-Free Nutraceutical Weight Management Product in an Asian Population

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ABSTRACT

Background: Obesity is now a global health problem. The purpose of this study was to evaluate a novel ephedra-free nutraceutical weight management system product.

Methods: Ninety-three subjects (male and female) entered a 30-day open-labeled trial involving consumption of 8 botanicals and 4 nutraceuticals in 3 pre-meal drink mixes and capsules. Given the difficulty of achieving a drink-mix placebo, no placebo was used. Comparisons were made between baseline and final (30-day) basis. The study population included normal (n=11), overweight (n=58) and obese individuals (n=24) as defined by body mass index (BMI). Pre and post trial assessments included weight, BMI, fat content, waist/hip measurements and blood chemistries (cholesterol, glucose, ketones).

Results: Eighty-seven subjects (94%) successfully completed the trial. The product was well tolerated and effective. Weight, BMI, fat levels, and waist-hip ratios of normal, overweight, and obese individuals were reduced in 91%, 87%, 71% and 56% of the subjects respectively (p<0.0001). Average weight loss was independent of gender, age, and degree of obesity: normal (1.32 kg, 2.9 lb), overweight (1.06 kg, 2.3 lb) and obese (1.10 kg, 2.4 lb) groups respectively. Complications were transient, largely gastrointestinal and

included altered stool formation (5%), reduced appetite (75%) and constipation (16%). Twenty-nine individuals (33%) had initial elevated blood cholesterol levels (216±3 mg/dl). At trial's end this group experienced a normalization of cholesterol levels (190±3 mg/dl, p<0.0001). Only 7 subjects (8%) had levels above 200 mg/dl, suggesting that a modification in lipid absorption, metabolism and/or disposition occurred. Individuals with normal cholesterol levels remained unaffected (178±2 vs. 176±2 mg/dl). Other blood chemistries were not altered.

Conclusion: This well-tolerated product facilitated generalized weight loss in 30 days, with an important, concurrent, cholesterol lowering benefit of surprising magnitude. Use of this product may provide a means of treating obesity and its related disorders.

INTRODUCTION

The new millennium marked the first time that the worldwide population of undernourished humans (1.2 billion) equaled that of the "over nourished."[1] The obesity pandemic causes significant morbidity and mortality with great social and financial implications. Its well-documented[2-8] ramifications in disease states include hypertension, diabetes, asthma, arthritis, cancer, and cardiovascular disease.

Recent reports indicate that individuals only slightly overweight (BMI 25-29.9) are also at a greater risk for these conditions, especially non-insulin dependent type II diabetes. Over 60% of the US adult population is either overweight (BMI 25–29.9) or obese (BMI > 30) and more than 22%–or 38 million–are in the latter category.[9] In 1998 51.6 billion dollars were spent in the US in direct costs associated with obesity; in 2000, one report placed this figure at $238 billion,

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an amount expected to increase proportionally.[10] Canadians and Europeans face similar health and financial catastrophes.

Traditionally, obesity has been a disease of affluence more common in Western nations. However, a growing need to address weight management is surfacing in Asian communities as they gather increased economic status and subsequent acquisition of Western diets.[11,12] A survey of men and women over twenty years of age by the Nanjing Medical University concluded that 30% of China's population is overweight.[13] The introduction of high-fat Western foods into a previously "low fat" society – as demonstrated in the United States[14] – has contributed to the problem.[15] This phenomenon is not limited to the United States and China. Many Asian cultures previously untainted by the western diet are finding obesity and its related diseases becoming the main focus and burden of their healthcare systems (Table 1).

Unfortunately, children and young adults often spearhead these obesity trends. Approximately 20% of the world's population of children live in China; today, 13% of China's 140 million urban children ages 7 to 14 are overweight, compared with just 3% 10 years ago. This figure is expected to double in the next 10 years given the more indulgent upbringing subsequent to China's "one child" policy playing a significant role. In a more recent study of 1,000 obese children from urban China, 30% had high blood pressure and over 40% suffered from fatty livers and high cholesterol. In Japan, 5 to 11% of schoolchildren age 6 to 14 show the prevalence of obesity.[18] In Taiwan, a study of 843 schoolgirls ages 10 to14 revealed that 65% wanted to be thinner and 38% had intentionally tried to lose weight.[20]

There are several approaches to weight reduction and management. For many patients, weight reduction regimes that focus on lifestyle modification, diet, and exercise prove temporarily effective. Others require more aggressive therapies. Weight loss medications may be appropriate for use in selected obese patients or those with co-morbid conditions. Pharmaceuticals are formulated to reduce energy intake, increase energy output, or decrease the absorption of nutrients. They have been effectively used as a primary strategy in the treatment of obesity, but are not without complications. In 1997, two popular prescription drugs, dexfenfluramine and fenfluramine, were removed from the market after heart-valve defects were noted in users and confirmed in subsequent studies in the United States.[21]

Various bariatric surgical procedures including gastric restriction (gastric banding, vertical banded gastroplasty) bypass (Roux-en-Y, bilopancreatic diversion), and stomach "stapling" are employed for intervention, reserved primarily for serious and life-threatening cases. Even the most common are not without risk, and one recent study documented deaths related to liposuction.[22]

Nutraceuticals or natural botanical-derived-over-the counter (OTC) preparations offer an alternative to pharmaceutical and surgical approaches; while pervasive, they are not widely reported to be effective. The majority are based on natural stimulants. The botanical-based ephedrine alkaloids (ephedra, and ma huang) are the most popular. While some believe that natural stimulants are inherently safe, the safety of these medications has recently been called into question,[23-26] with reports of ephedrine toxicity, myocarditis and death. Similarly, botanical-based diuretics such as Uva Ursi (*Arctostaphylos uva-ursi*) have been included in "fad" weight loss systems temporarily reducing weight with the reduction of total body water. However, short-term use has been shown to be ineffective and long-term use deleterious.[27, 28]

Diet, exercise and lifestyle modifications remain the cornerstones of obesity treatment. Having safe alternatives to pharmaceutical therapy that may delay or aid in the management of this disease and its sequellae would be of great benefit. The purpose of this study was to evaluate the efficacy of such an alternative – a novel non-thermogenic nutraceutical weight reduction product – in an adult Asian population.

METHODS

Participant Profile: Ninety-three adult Cantonese individuals (34 men, 59 women) were selected from the general Hong Kong population to participate in a nutraceutical-based ephedra-free and stimulant-free weight reduction system in a 30-day open-labeled trial with no placebo control. Subjects were recruited through local newspaper solicitation and were not required to have a commitment to weight loss. To further mimic a "real life" situation, the selection criteria were minimal and limited to general "good health" as determined solely through oral interview. Selection specification included general lack of an exercise

Table 1: Obese-overweight population ratios of selected asian countries[16-19]

Country	Year	Age (years)	% Obesity		% Overweight	
			Male	Female	Male	Female
Hong Kong	1990	18-65	2.2	4.8	10	27.9
Japan	1990-94	35-64	1.9	2.9	24.3	20.2
	1997	9	9.7	8	NA	NA
Republic of Korea	1994-1997	20-60+	1.4	1.9	20% Population	
Urban Malaysia	1991-1994	18-60	4.7	7.7	24	18.1
Philippines	1993	≥ 20	1.7	3.4	12.7	15.2
Thailand	1991	≥ 20	1.7	5.6	12	19.5
Taiwan	1994-1998	≥ 18	5.0	7.0	17.5	15.9

regime and precluded use of any other weight reduction supplement, pharmaceutical or otherwise within the period of the trial. In this manner, females (n = 59) and males (n = 34) ranging in age from 18 to 49 years were selected and stratified based on sex, age (females: 18–30, 31–44 and > 45 years old; males: 18–39 and >40 years old), percent overweight (either <15% or >15% overweight) and body mass index (normal: BMI < 25 kg/m², overweight: BMI> 25–29.9 kg/m², and clinically obese: BMI>30 kg/m²).

Assessments made at baseline and after the trial included weight, BMI, fat content, waist and hip measurements (waist-hip ratio), blood pressure, and blood chemistries (cholesterol, glucose, ketones). Weight and BMI were determined using a digital scale and a metric measuring device. Before and after waist and hip measurements were made by using a standard metric tape measure with the same individual performing these measurements before and after the trial period in order to better address common error. Fat content was determined by impedance (Tanita Corp: Arlington Heights, IL) and confirmed periodically via skinfold caliper of biceps, triceps, subscapula, and iliac crest (Caldwell, Justiss & Co.: Fayetteville, GA) and the Durnin/Wormersley formulas. Blood chemistries were obtained from the second drop of blood from a finger stick using devices that measured both glucose and ketones (Abbott Laboratories: Bedford, MA) or glucose and cholesterol (Roche Diagnostics Corp: Indianapolis, IN). All devices were calibrated prior to and during use, and the glucose reading was used for accuracy confirmation between measuring devices. Blood pressure and heart rate were assessed using a sphygmomanometer and stethoscope or a digital monitor (Omron Healthcare: Vernon Hills, IL).

Participants were instructed to refrain from exercising, altering their normal diets, or changing their lifestyles in any manner that might accentuate weight reduction. Questionnaires regarding their "well-being" were given prior to and following the 30-day period of the trial. A general questionnaire concerning palatability and tolerance was administered post-trial. In addition, the subjects kept a daily log of symptoms and were contacted periodically throughout the study period to assure compliance and to monitor and address any health concerns. Informed consent was obtained in writing and the subjects were compensated for their participation.

Materials: The product consisted of dry drink mixtures or capsules containing the following ingredients: *Aloe barbadensis* (Active Aloe,™ Aloecorp: Broomfield, CO), L-Carnitine (carnipure,®Lonza: Fair Lawn, NJ), *Fucus vesiculosis* (Stryka Botanics: Hillsborough, NJ), *Gymnema sylvestre* (Actives International: Ramsey, NJ), *Lepidium meyenii* (Inca Gold,™ Rainforest Phytoceuticals: Delmar, NY), *Passiflora incarnata* (American Ingredients: Anaheim, CA), poly-D-glucosamine (Liposan Ultra,™ Vanson: Redmond, WA), Soy protein concentrate (Soyarich:® Central Soya Co: Ft Wayne, IN), *Uncaria guianensis* (Vinicol,™ Rainforest Phytoceuticals), and

Stevia rebaudiana (Stryka Botanics: Hillsborough, NJ). Also included was a powdered mixture (Nutratech: Fairfield, NJ) that contained bis(maltoato)oxovanadium(IV), chromium polynicotinate, and the recommended nutritional intake (RNI) of 21 vitamins and minerals.

This low-calorie nutritionals and fiber product was designed to limit fat absorption and to produce satiety before meals, thereby addressing both weight loss and the complications associated with obesity that contribute to overall morbidity and mortality, specifically elevated cholesterol.

The materials were obtained from the site of origin (*e.g.*, *Uncaria guianensis* from the Amazon River basin of Perú) or from major supply houses in the United States and accompanied with certificate of analysis. Samples were requested prior to final selection and on average, five of each of the fourteen ingredients obtained. Each sample was tested for purity primarily by precipitate assay and/or relevant biological activity (ie: 2,2'-dipyridyl-2-pyridylhydrazone radical species scavenging ability: DPPH), enzyme linked immunoabsorbent assay (ELISA), or high performance liquid chromatography (HPLC). Additionally, published data concerning certain "brand" ingredients and/or nuclear magnetic resonance (NMR) imaging data were supplied by some manufacturers and taken into consideration in the selection process.

Stimulants such as ephedra and caffeine, and diuretics such as *Arctostaphylos uva-ursi* were excluded from the formulation.

Program Description: Ingredients were blended and packaged as capsules or powdered drink mixtures (3) to be taken daily 15-30 min before either meals or bedtime. All packaging was of food-grade quality (drink mixtures), or FDA-certified pharmaceutical encapsulation (Clinical Encapsulation Services: Schenectady, NY), and manufacturers were ISO9000-certified.

In accordance with the policies of the Hong Kong Health Authority, drink mixtures were clearly labeled for content and directions in simplified Chinese and English. Both the mixtures were packaged for daily use specifying consumption times (i.e. 15 to 30 minutes before either mealtimes or bedtime), directions (mix well in six to eight ounces water) and were color-coded. The daily capsules were secondarily packaged in aluminum film pouches according to their time of use, similarly labeled and color-coded. The number of drink mixtures and packaged capsules corresponding to the requirements for a single day's use were boxed together and dual-labeled for "daily" use. Thirty of said boxes were assembled together to represent the materials needed for the trial and distributed to each participant. All packaging was done in the United States and shipped trial-ready to Hong Kong.

Statistical Analysis: Results were compared on a paired basis, before and at the conclusion of the treatment period, using either a Student's t-test or a Mann-Whitney U test based on whether the data was distributed in a gaussian manner.

RESULTS

Component Evaluations: On average, 5 samples of each ingredient were submitted for inclusion and evaluated "in-house" as previously described. Individual and ingredient-specific methodologies identified several samples to be 2 to 24 times more assay-effective than their counterparts. These findings were additionally supported by previously published results, submitted nuclear magnetic resonance (NMR) imaging data, or other relevant functional assays (i.e. fat absorption capacity).

Outcome Measures: Fat content as determined by impedance and caliper (Durnin/Wormersley calculation) was found to be in near agreement ($\pm$1%); ease of use of the impedance-based system made it the preferential testing method for the study. Similarly, blood glucose values as determined by both devices were consistently found to be in near agreement (90.3$\pm$7.4%) indicating proper functioning and reliability for subsequent measurements.

Participant Compliance: Eighty-seven of the 93 subjects (93.6%) completed the trial, complying with the trial criteria. The remaining 6 were excluded from the final analysis because they either initiated a regular exercise program ($\geq$3x/wk: n=1), altered their diets in a significant manner (consumed less fatty food: n=2), or regularly used the drink mixtures as meal replacements (n=3).

Weight Reduction: Over the course of the study 91 percent (79 of 87) of the participants reduced their weight an average of 1.25 kg (2.75 lbs) without exercise or diet modification (p<0.0001). This reduction was independent of BMI status, sex, or age, although there was a 26% greater response from the $\geq$40 than the 18-29 year-old age groups. The largest single weight reduction over the course of the study was 5.0 and 3.8 kg (11 and 8.4 lbs) in a male and female with the average per gender being 1.35 and 1.21 kg (2.97 and 2.65 lbs) respectively. Eight of the 87 participants (9%) experienced an increase in weight, on average 0.35 and 0.78 kg for males and females respectively (Table 2).

BMI and Fat Reduction: Eighty-seven percent (76 of 87) of the participants reduced their BMI on average 0.43 p<0.0001). Three of the 24 individuals (13%) categorized as clinically obese (BMI >30 kg/m2) reduced their BMI to the lower classification (BMI 29.9-25 kg/m2). Seven clinicaly obese participants reduced their BMIs to normal classification (BMI <25 kg/m2). Sixty-two of 87 participants (71%) reported an average fat loss of 0.67 kg (1.47 lbs) at the completion of the study (p<0.0001). The highest individual recorded loss was 6.8 kg (15 lbs).

Waist-Hip Measurements: The average circumferential hip and waist reductions were 1.88 cm (0.74 in) and 0.44 cm (0.17 in) respectively. The highest and lowest single individual reductions were -12 cm (4.72 in) and -11 cm (4.33 in), and +8 cm (3.15 in) and +6 cm (2.36 in) respectively. No significant difference was noted based on sex, age, weight, or BMI.

Ketones and Glucose: No significant change in ketones appeared in any category, indicating the participants did not fast during the study. Similarly, glucose values did not change except in those individuals who did not fast prior to testing.

Cholesterol: Pre-trial blood cholesterol assessment revealed that one third of the participants (29/87) had levels exceeding 200 mg/dl, a primary indicator of concern for cardiovascular disease. These participant's average blood cholesterol values were 216$\pm$3 mg/d, while the remainder of the population averaged 178$\pm$2 mg/dl (Figure 1). At the conclusion of the 30-day trial, those subjects whose levels were initially normal remained so (176$\pm$2 mg/dl). In contrast, those subjects whose initial cholesterol levels were elevated enjoyed a substantial reduction: average values fell into the normal range (190$\pm$3 mg/dl, p<0.0001). Of the 29 subjects (33%) who had initial cholesterol levels greater than 200 mg/dl, only seven (8%) remained above this marker at the conclusion of the trial.

Cardiovascular Assessments: Blood pressure and heart rate was determined in all subjects prior to and following the trial period. Values before and after the trial were not significantly different (Table 3).

Tolerance and Compatibility: The product was well tolerated by participants. The most common complaints were gastrointestinal: constipation (16%), flatulence (13%) or non-specific problems (8%). All gastrointestinal symptoms were transitory in nature and usually resolved within 3 to 5 days. Most participants reported that they were less hungry at meal times (77%), less hungry throughout the day (75%) and subsequently could eat less (67%) to feel sated. However, 9%

Figure 1: The effect of study product on blood cholesterol levels.
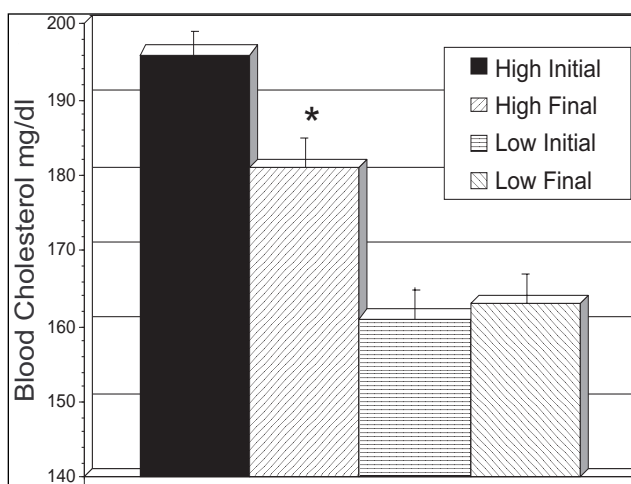
Those participants whose cholesterol levels were high at the beginning of the study ($\geq$200mg/dl, n=29, "High Initial") demonstrated a significant reduction in cholesterol (P<0.0001) at the conclusion of the 30 day study period. Those participants whose cholesterol levels were normal at the beginning of the study (< 200mg/d, n=58, "Normal Initial") were unaffected.

Table 2: Average weight loss (kg) as determined by BMI, sexes and ages.

Category	BMI (kg/m^2)			Age Group		
	≥30	29.9-25	<25	18-29	30-39	≥40
Total	1.10	1.06	1.32	1.10	1.21	1.49
Male	0.88	1.55	1.95	1.47	1.06	1.82
Female	1.26	1.14	1.12	0.98	1.30	1.33

reported an increase in appetite, an increase in consumption or both. The majority of the subjects (95%) reported the system to be safe and were subsequently motivated to continue reducing their weight following the trial (69%).

Forty-five (52%) subjects had previously tried other weight loss products, either pharmaceuticals as prescribed by their physician, or over-the-counter "natural" products. In the latter category, a United States ephedra-based product (USEBP: Herbalife International: Los Angeles, CA) was the most popular (35% of OTC products used), but with limited satisfaction and preference. Questionnaire data is summarized in Table 4. Overall, 53% of the participants reported satisfaction with the outcome of the trial.

Well-being Questionnaire: The majority of the respondents reported "no change" when comparing the pre and post trial data. However:

• 23% reported an increase in ability to exercise; 4% reported a decrease;

• 37% reported an increase in their ability to achieve things; 4% experienced a decrease; and

• 29% believed that use of the product increased their attractiveness to others; 9% reported the opposite.

DISCUSSION

Despite design limitations, specifically lack of placebo control, the nutraceutical and botanical system facilitated a reliable weight loss in the study population: 9 of 10 subjects lost weight. The amount of weight loss was not dramatic but nevertheless consistent with reductions associated with sustained benefits with continuation. The amount of weight loss is also consistent with those values expected for effective pharmaceuticals in this Asian population.[2] The study reinforces, however, that claims of dramatic weight loss with nutraceuticals have not been substantiated in large population studies.

In this study, subjects lost weight with no specific alteration in diet or exercise. These approaches are regarded as critically important components of obesity management. One would anticipate that if these strategies were also

Table 3: Effects of study product on blood pressure and heart rate (HR).

Group	Mean Pre Trial Measurements			Mean Post Trial Measurements		
	Systolic	Diastolic	HR	Systolic	Diastolic	HR
Male	135	86	77	130	83	70
Female	122	80	77	122	84	75
BMI ≥30	133	89	79	129	86	73
BMI <30	124	80	76	123	82	75
ALL	128	82	77	125	83	73

Table 4: A survey of comparative weight reduction products.

Diet Plans	# Users	# Satisfied	% Satisfied	# Preferring other products	% Preferring ephedra-free products
Rx	14	5	35.7	4	71.4
USEBP*	12	4	33.3	1	91.7
Other	22	7	31.8	6	72.7
Total All	48	16	33.3	11	77.1

*USEBP: United States Ephedra-Based Product, Herbalife® International Inc., Los Angeles, California.

included, further benefits would occur. However, the goals of this study were to assess the ability of the product to induce weight loss in a "real world" situation. This product could be used to initiate a sustained and effective approach to weight management. Indeed, in the post-trial questionnaire, a number of individuals stated that they were now motivated to continue to control their weight.

Baseline weight was not a determinant of overall weight loss, with a consistent decrease observed among all groups. In the real world conditions of the trial, the reduction was reliable, 9 out of 10 subjects lost weight regardless of baseline values. Thus, even those with normal or slightly elevated baseline weights reaped benefits. With no placebo one could propose that this occurred by chance. However, consistency of response suggests otherwise. Several articles in the *New England Journal of Medicine* challenge the notion of a placebo effect and the influence it has over observational studies.[28-30] Indeed, for many trials the inclusion of a placebo group does not alter data interpretation.[28,29] Additionally, designing an adequate and meaningful placebo for various drink mixes and capsule combinations is complex and may not achieve the desired effect, the elimination of changes that result purely from

chance. For example one goal of the drink mix formula was to produce satiety before meals based on a feeling of "fullness." It is conceivable that an otherwise biologically inert substance could elicit a similar response and affect food consumption. In that setting, is it an accurate placebo – or another means to deliver the desired response? Related to this issue, some participants through the third week of the trial reported, surprisingly, that their food consumption had increased. This was not due to any decrease in feelings of satiety. In fact the majority of the participants reported a decrease in appetite. Rather, this response more likely reflects a cultural belief that a decrease in appetite is an indication of illness that historically is addressed in Asian societies by increased food consumption. Thus, despite an increase in caloric intake, the majority of the subjects experienced a reduction in weight.

Compliance was noticeably more effective in older than younger participants. This age-related effectiveness was not due to differences in baseline obesity or any fundamental differences between groups. We speculate that it may reflect compliance: younger participants are more likely than elders to consume products in a discontinuous manner, limiting their efficacy, whereas their elder counterparts are more likely to be attentive and comply better with directions.

This weight management product was designed to lower cholesterol levels in addition to weight as part of a global approach to manage obesity-related disorders.[2,7,8] For example, the Andean cruciferous vegetable maca has high levels of isothiocyanates and sitostanols thought to lower cholesterol levels, contribute to cardiovascular health, and reduced cancer risk.[32-34] The product also contains chitosan to limit fat absorption and soy protein, recommended by the American Heart Association as a means of lowering cholesterol levels. Nevertheless, we were surprised at the magnitude of the cholesterol-lowering response. At the beginning of the study, 33% had cholesterol levels that exceed safe levels (>200 mg/dl). This population is normally encouraged to modify their diet and/or initiate an exercise program to bring their cholesterol levels below 200 mg/dl. Often, this is difficult to achieve. For some patients pharmaceutical strategies must be adopted to lower cholesterol levels or they will remain at risk for cardiovascular disease. This is true for Asian as well as Western populations. In this high-risk group, the weight management product produced a 26 mg/dl average reduction in cholesterol levels over the 30-day period. Indeed, the number of participants with high cholesterol decreased from 33% to 8%. Importantly, the product did not affect cholesterol levels in those with a normal level before trial. As discussed above, it would be useful to repeat these studies in a design with a placebo group or a wash-out protocol. Given the magnitude of the cholesterol response, a greater population base and a study of greater duration would also be worthwhile.

This weight loss product was designed to avoid the potential health hazards associated with ephedra, stimulants and diuretics. Serious cardiovascular complications have been associated with these components, including stroke, myocardial infarctions, myocarditis, and sudden death.[23-28] This has led to a growing concern amongst regulatory (FDA) and health care agencies as to the safety of numerous weight loss products. The purpose of this report is not to debate the validity of these concerns, but rather to determine if an ephedra-free product can be effective. In the post-trial questionnaire it was clear that some participants had tried other weight loss strategies, but in general were not encouraged by their results. By comparison, this product was well received and its approval rating was approximately double that for pharmaceutical or other nutraceutical regimes in those who had tried them. It is not known why this program was preferred given the modest effect on weight loss. We speculate that it may reflect the subjects' feeling of well-being.

Safety must always be a concern with any dietary supplement. The product was associated with alterations in gastrointestinal system activity, primarily constipation (16%) and flatulence (13%). These are not unexpected for a change in diet, were mild and transient in nature, and subsided within days of the program's initiation. Most noticeable was loss of appetite. Also encouraging were other assessments of safety and tolerance: blood pressure and heart rates were not significantly altered, the cholesterol-lowering response was regarded as an important and significant benefit, and other evaluations of blood chemistry (glucose and ketones) were unaffected. Thus, while these assessments of safety and tolerance were limited, they highlight that use of the product created no systemic complications or adverse effects.

In summary, this study suggests that an ephedra-free nutraceutical system can initiate reliable weight loss without dietary pattern changes or initiation of an exercise program. The beneficial effects on normalizing blood cholesterol levels in those individuals at high risk for cardiovascular disease suggests that this approach may be useful for initiating a change in lifestyle for managing obesity and its related disorders.

REFERENCES

1. Brown LR, Flavin C, French H *et al. State of the World 2000.* 1st ed. The Worldwatch Institute. New York: WW Norton and Co: 2000.

2. Inoue S, Zimmet P. *The Asia-Pacific perspective: redefining obesity and its treatment. Melbourne:* Health Communications Australia, Pty Ltd; 2000.

3. Amos A, McCarty D, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabetic Med.*1977;14:S1-85.

4. Camargo CA Jr, Weiss ST, Zhang S, *et al.* Prospective study of body mass index, weight change and risk of adult-onset asthma in women. *Arch Int Med.* 1999;159:2582-2588.

5. Sturmer T, Gunther KP, Brenner H .Obesity, overweight and patterns of osteoarthritis: the Ulm osteoarthritis study. *J Clin Epid.* 2000;53:307-313.

6. Ford ES. Body mass index and colon cancer in a national sample of adult US men and women. *Amer J Epid*.1999;150:390-398.

7. Calle EE, Thun MJ, Petrelli JM, *et al.* Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med*. 1999;341:1097-1105.

8. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic.* Geneva. WHO;1998.

9. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obes*. 1998; 22:39-47.

10. Update: The Healthcare Costs of Obesity. Paper presented at the American Obesity Association's 2nd Annual Conference - Obesity: The Public Health Conference.Sept.13,2000. Washington, DC.

11. Zimet ZP, Dowes G, Serjeanston S, *et al.* The epidemiology and natural history of NIDDM: lessons from the South Pacific. *Diabetes Metab Rev*.1990;6:91-124.

12. Dowes GK, Hodge AM, Zimmet PZ. Paradise lost: obesity and diabetes in Pacific and Indian Ocean populations. In: Angel A, *et al., eds.* Progress in Obesity Research. London: John Libbey & Co;1995.

13. Interesting Facts and Figures. *Express China News*. 1998;98;4.

14. Norris J, Harnack L, Carmichael S, *et al.* US Trends in Nutrient Intake: the 1987 and 1992 National Health Interview Surveys. *Am J Pub Health*. 1997;87:740-746.

15. Turner M "Too stuffed to Jump." *Time International Magazine.* 1996;148:13.

16. Ismail MN, Zawiah H, Chee SS,*et al.* Prevalence of obesity and chronic energy deficiency (CED) in adult Malaysians. *Malay J Nutr*. 1995; 1:1-9.

17. Yoshiike N, Matsumura Y, Zaman MM, *et al.* Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990-1994. *Int J Obes*. 1998;22:684-687.

18. Ito K, Murato M.Diagnostic criteria of childhood obesity. *Jap J Peds*. 1999;52 (suppl):1182-1196.

19. Ko GTC, Chan JCN, Woo J, *et al.* Simple anthropomorphic indexes and cardiovascular risk factors in Chinese. *Int J Obes*. 1997;21:995-1001.

20. Wong Y, Bennink M, Wang M, & Yamamoto S. Over concern about thinness in 10- to 14-year-old schoolgirls in Taiwan. *J Am Diet Assoc*. 2000;100:234-236.

21. Gardin JM, Schumacher D, Constantine G, *et al.* Vascular abnormalities and cardiovascular status following exposure to dexfenfluromine or phetermine/fenfluromine. *JAMA*. 2000;283:1703-1709.

22. Ginsberg MM, Gresham L. Deaths related to liposuction. *N Engl J Med*. 1999; 341:1000-1003.

23. Zaacks SM, Klein L, Tan CD, *et al.* Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol*. 1999;37:485-489.

24. Leikin JB, Klein L. Ephedra causes myocarditis. *J Toxicol Clin Toxicol. 2000;* 38:353-354.

25. Gurley BJ, Gardner SF, White LM, Wang PL. Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing *Ephedra sinica* (ma huang). *Ther Drug Monit*. 1998;20:439-445.

26. World Health Organization (WHO): *World Health Report 2000*.

27. Schulz V, *et al. Rational Phytotherapy.* New York: Springer-Verlag;1998;223.

28. *Fascicule 2: Uvae Ursi Folium.* In: ESCOP monographs. Exeter, UK: European Scientific Cooperative on Phytotherapy; 1997.

29. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *New Engl J Med. 2000;* 342: 1878-1886.

30. oncato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the heirachy of research designs. *New Engl J Med. 2000; 3*42:1887-1892.

31. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New Engl J Med.* 2001;344:1594-1602.

32. Dini F, Migliulo G, Rastrelli L, Saturninbo P, Schettino O. Chemical composition of *Lepidium meyenii*. *Food Chemistry.* 1994; 49:347-349.

33. Hecht SS. Chemoprevention of cancer by isothiocyanates, modifiers of carcinogen metabolism. *J Nutr.* 1999;129:768S-774S.

34. Ramjiganesh T, Roy S, McIntyre JC, Luz Fernandez M. The hypocholesterolaemic effects of sitostanol in the guinea pig are in part related to changes in hepatic lipids and lipoprotein composition. *Br J Nutr.* 2001; 85:165-172.