ORIGINAL RESEARCH

EFFECT OF A PROPRIETARY *MAGNOLIA* AND *PHELLODENDRON* EXTRACT ON WEIGHT MANAGEMENT: A PILOT, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

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Objective • To determine the efficacy of a dietary supplement ingredient containing proprietary extracts of *Magnolia officinalis* and *Phellodendron amurense* in helping overweight, otherwise healthy, premenopausal female adults, who typically eat more in stressful situations manage their body weight.

Design • Randomized, double-blind, placebo-controlled clinical study.

Setting • Miami Research Associates, a clinical research organization consisting of 32 board-certified physicians, Miami, Fla.

Subjects • Healthy, overweight (BMI 25 to 34.9), premenopausal female adults, between the ages of 20 and 50 years, who typically eat more in response to stressful situations and scored above the national mean for women on self-reported anxiety.

Interventions • Two-hundred-fifty-mg capsules or identical placebo capsules 3 times a day for 6 weeks.

Main Outcome Measures • Salivary cortisol levels, weight change, psychological measures of stress and anxiety.

Results • Twenty-eight subjects completed the study. Extracts of *M officinalis* and *P amurense* were well tolerated. There was a significant weight gain during the study for the placebo group ($P < .01$), but no significant weight gain for the group receiving extracts of *M officinalis* and *P amurense* ($P < .89$). Paired *t*-tests comparing baseline to post-treatment weight showed an average gain of 1.5 kg in the placebo group and no change in the treatment group ($P = .89$). When groups were divided into gainers (ie, participants who gained at least 1 kg or more) and maintainers or losers, 75% of the control group were gainers versus 37% of the treatment group ($P < .04$). There was a nonsignificant trend for lowered average cortisol in the treatment group at the end of the study (group X time interaction, $F = 1.1$, $P < .15$). This difference was due to a treatment effect on evening cortisol. There was a marginally significant group X time interaction ($P = .06$), showing the treatment group tended to have lower levels of cortisol in the evening, whereas the control group tended to have higher levels of cortisol in the evening. Bedtime cortisol levels decreased in the treatment group and increased in the placebo group. Participants in both the treatment and placebo groups had improved scores on a number of psychological measures during the study. There was a correlation between perceived stress and weight change.

Conclusion • The results of this pilot clinical study indicate that obese subjects who eat in response to stress may benefit from taking a dietary supplement ingredient containing proprietary extracts of *M officinalis* and *P amurense*. The mechanism of action appears to be through reduction of cortisol levels and possibly perceived stress, thereby helping participants maintain body weight. The sample size was small, however, and there was higher attrition in the control group than in the treatment group.

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Obesity is a growing health problem in the United States and in other developed nations. The World Health Organization (WHO) reports that more than 1 billion adults worldwide are overweight (ie, have a body mass index [BMI] of more than 25 kg/m^2) and that 300 million adults are obese (ie, have a BMI of more than 30 kg/m^2).[1] A recent review of several national surveys by Hill et al concluded that the obesity epidemic in the United States shows no signs of abating and that there is an urgent need to counter the environmental forces that are contributing to gradual weight gain in the population.[2] The authors cited the availability of good-tasting, inexpensive, energy-dense foods that are consumed in large quantities and reduced physical activity as key contributors to an "energy gap."[2] Although the need for safe and effective weight-management products is increasing, there is a lack of safe and effective products in the marketplace. Historically, weight management products have contained stimulants, which work as appetite suppressants.

Recent regulatory action by the US Food and Drug Administration (FDA) to ban dietary supplement products that contain ephedra alkaloids and over-the-counter products that contain phenylpropanolamine underscores that the unacceptable risks of using stimulants for their appetite-suppressing effects outweigh their benefits.

In addition, weight regain following completion of a diet is an ongoing problem for many people. In 2003, The National Heart, Lung and Blood Institute at the National Institutes of Health (NIH) announced the initiation of a major, multi-center, clinical study with a primary objective of teaching patients how to keep weight off after successful dieting.[3]

Researchers at the University of California, San Francisco have shown a link between chronic stress and obesity.[4,5] A study on stress-induced eating by Epel et al showed that high cortisol reactivity in response to stress led to increased eating of high caloric foods and sweets.[5] Furthermore, people who identified themselves as "stress eaters" tended to gain weight over time and showed a worsening in their lipid profile.[6]

The hypothalamic-pituitary-adrenal (HPA) axis is an integrated system that maintains appropriate levels of glucocorticoids. Stressful stimuli can lead to marked increases in plasma concentrations of adrenocortical steroids by overriding the normal negative feedback control mechanisms. Cortisol increases the availability of glucose through hepatic gluconeogeneses and the release of glucose substrates from fat cells and muscles. The uptake of glucose is inhibited, resulting in hyperglycemia and hyperlipidemia.[7] Cortisol increases the availability of glucose through hepatic gluconeogeneses and the release of glucose substrates from adipocytes and muscles. The uptake of glucose is inhibited, resulting in increases in plasma glucose and lipids.[8]

NP 33-39 (Relora, Next Pharmaceuticals, Inc, Irvine, Calif) is a proprietary combination of a patented extract of Magnolia officinalis and a patent-pending extract of *P amurense*. The use of the magnolia fraction for stress and cortisol-related weight control, restlessness, and sleeplessness is covered under United States Patent No 6,582,735. A patent is pending on the phellodendron extract. The recommended dosage is three 250-mg capsules per day.

The extract of *M officinalis* and *P amurense* has been studied in a series of animal model and unpublished, open-label, clinical studies that have shown that, individually, the extracts have anxiolytic properties and that when used in combination the extracts reduce self-reported stress and promote restful sleep.[9] In addition, the magnolia extract component in the formulation was shown in an unpublished clinical study to reduce morning and evening cortisol levels in subjects with elevated cortisol levels.

OBJECTIVE

The primary objective of this pilot clinical study was to determine the ability of NP 33-39 to help overweight, otherwise healthy, premenopausal female adults who typically eat more in stressful situations manage their body weight.

METHODS

Study Design

This study was a 6-week, double-blind, placebo-controlled trial. Advertisements were placed in English and Spanish in local newspapers in the Miami, Fla, area. The advertisements read, "Is stress making you eat? You may qualify to participate in a research study of a nutritional supplement for people who eat more during stressful situations. To qualify, you must not be taking medications for depression or anxiety, be overweight but in good general health, be 20 to 50 years of age, be a premenopausal female." The study was approved by an institutional review board (IntegReview Ethical Review Board, Austin, Tex), and all participants signed an informed consent form.

Inclusion criteria were healthy, overweight (BMI 25 to 34.9), premenopausal female adult between the ages of 20 and 50 years who typically eats more in response to stressful situations and scored above the national mean for women on self-reported anxiety. Exclusion criteria were

- a personal history of heart disease, uncontrolled high blood pressure, renal or hepatic impairment/disease, type 1or type 2 diabetes, psychiatric disorders, cancer, sleep disorders, glaucoma, difficulty urinating, gastric ulcer or reflux disease, a seizure disorder, unstable thyroid disease, pregnancy, lactation, or any medical condition deemed exclusionary by the medical staff;
- scores positive for binge eating disorder based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for diagnosis;
- scores positive for major clinical depression using the Hamilton Depression Scale;
- currently taking monoamine oxidase inhibitors (MAO-I), anxiolytics, psychotropics, stimulants, or steroid hormones;
- use of weight loss supplements or drugs within the previous month;
- weight loss or gain of greater than 3 kg within the previous 3 months;
- uncontrolled hypertension (systolic >140 mm Hg, diastolic >90 mm Hg);
- pregnant, lactating, or planning to become pregnant during the study;
- not using an acceptable form of contraceptive device;
- current use of any dietary supplement purported to alter stress hormones; and
- prior diagnosis of post-traumatic stress disorder.

Forty-two participants were randomized to either the treatment or control group. Blood was taken for laboratory analysis at the start of the study and again at day 42. Participants were weighed and completed assessments for stress using the Cohen Perceived Stress Scale, for anxiety using the Spielberger State-Trait Anxiety Index (STAI), and for mood using the Positive and Negative Affect Scale (PANAS) and the Center for Epidemiological Studies Depression Scale (CEDS) at the beginning, mid-point, and end of the study. Salivary cortisol levels were taken 3 times a day

(ie, upon waking, 30 minutes post-waking, and at bedtime) for 3 days at baseline and then again for 3 days at the end of the treatment period. A 3-day (2 working days and 1 non-working day) food diary was given at baseline and post-treatment.

Participants were asked to follow their typical diets and exercise levels. No dietary or exercise counseling was provided. Each participant was encouraged to maintain any current exercise program, and physical activity levels were quantified with the Framingham Physical Activity Index.

Safety assessments included a comprehensive metabolic panel, complete blood count with differential, and blood pressure and heart rate evaluation at the beginning and end of the study. Adverse events were recorded throughout the study.

Statistical Plan

Repeated measures analysis of variance (ANOVA) tests were used to test for group (treatment vs control) and time (baseline, end of study) interactions. Midpoint changes were not measured for most outcomes. Paired *t*-tests were used to compare weight gain and weight loss for each subject. Given the *a priori* hypotheses that the treatment group would show greater improvements, results are presented with 1-tailed *P* values for findings that were as predicted and are indicated by an asterisk in the text below. For results that were not predicted, 2-tailed *P* values were used.

RESULTS

Study Population

As shown in Table 1, there were no significant differences in the treatment and control groups at baseline in age, BMI, and waist:hip ratio (WHR). The treatment group was 100% Hispanic and the control group had 1 black, 1 white, and 18 Hispanic participants.

Eighteen participants in the treatment group and 10 participants in the control group completed the study. Nine subjects, 8 in the control group and 1 in the treatment group, were lost to follow-up. Five subjects were early terminators for various reasons. The 14 non-completers (ie, drop-outs and early terminations) were compared to the 28 completers on baseline variables using *t*-tests. The only significant difference between groups was that the completers showed significantly greater physical activity at baseline. It is unclear why there were more dropouts in the control (placebo) group than in the treatment group, but it could have been that those in the control group did not perceive any beneficial effects and were not interested in continuing the study for the full 6 weeks.

TABLE 1 Subject Demographics

Group Statistics

Group		N	Mean	SD	SEM
Age	Control	20	38.45	5.960	1.333
	Relora	22	38.59	7.028	1.498
BMI	Control	20	30.8600	4.25099	.95055
	Relora	22	31.6818	3.86679	.82440
WHR	Control	20	.8050	.07790	.01742
	Relora	22	.8177	.08023	.01711

BMI=body mass index; WHR=waist:hip ratio

Safety

Three participants dropped out because of side effects. The first participant complained of heartburn, shaking hands, perilabial numbness, sexual dysfunction, and thyroid dysfunction, and the study physician judged that the effects were "possibly related" to treatment. The second subject complained of fatigue and headache, and the study physician judged that the effects were "probably not related" to treatment. The third participant was in the control group and complained of irritability, abdominal bloating, and fatigue. The study physician judged that these side effects were "probably not related" to the treatment (placebo). There were no significant changes in metabolic profile laboratory values during the study in either group. There was a significant decrease ($P = .04$) in systolic blood pressure in the treatment group compared to the placebo group. The mean systolic pressure decreased by 5 mm Hg in the treatment group, compared to a mean increase of 3 mm Hg in the placebo group. This could indicate a potential secondary benefit of *M officinalis* and *P amurense extracts*. There were no significant changes over time in diastolic blood pressure.

Efficacy

There was a significant weight gain during the study for the placebo group ($P < .01$), but no significant weight gain for the treatment group ($P < .89$). Paired *t*-tests comparing baseline to post-treatment weight show an average gain of 1.5 kg and no change in the treatment group ($P = .89$). Analysis of covariance (ANCOVA) testing for weight changes in each group, controlling for baseline BMI, showed that the effects persisted ($F = 4.0$, $P < .03$). When groups were divided into gainers (gained at least 1 kg or more) and maintainers or losers, 75% of the control group were gainers vs 37% of the treatment group ($P < .04$). The numbers in each cell, however, are small, and chi squares (ie, exact tests) are difficult to interpret with less than 5 in one cell. The distribution of weight change in the control and treatment groups is shown in Figures 1 and 2, respectively. There were large and statistically significant reductions in caloric intake for both groups. When macronutrients were examined separately, there were significant reductions in protein, fat, and carbohydrate intake for both groups but no differences between the groups.

There was improvement in all of the psychological measures across the groups. Both groups decreased significantly in both state and trait anxiety ($P < .001$) and in negative mood over time ($P < .01$) with no significant differences between the groups. There was a large decrease in perceived stress over time in both groups ($P <. 0001$). Participants who maintained weight had significantly lower negative mood scores than participants who gained weight ($F_{1,16} = 6.5$, $P < .02$).

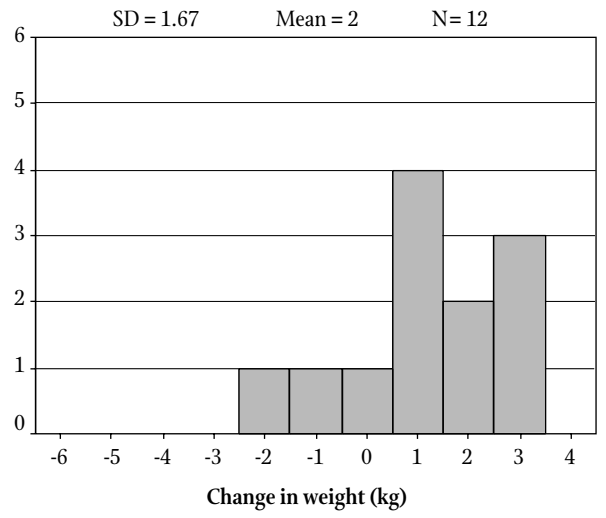

FIGURE 1 Distribution of Weight Change in the Control Group

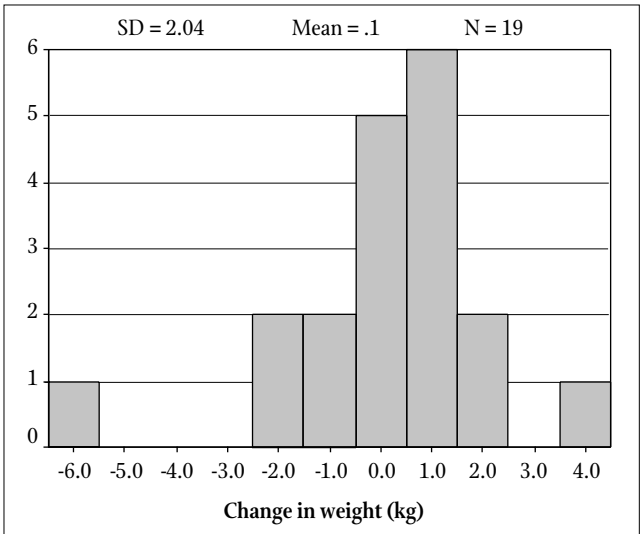

FIGURE 2 Distribution of Weight Change in the Treatment Group

Cortisol for each assessment period (baseline and end of study) was averaged across time points and days ("average cortisol") and was averaged across times of day (average morning cortisol, and average evening cortisol) for the 3 days. There was a nonsignificant trend for lowered average cortisol in the treatment group at the end of the study (group X time interaction, F = 1.1, $P < .15$). This difference was because of a treatment effect on evening cortisol. There was a marginally significant group X time interaction ($P = .06$), showing that the treatment group's levels of evening cortisol tended to decrease and the control group's tended to increase. These within-group changes over time were tested with paired *t*-tests and were not significant, suggesting that the changes in both groups in opposite directions is driving the interaction rather than changes in just one group (ie, it is not due solely to an increase in the control group, or to a decrease in the treatment group). Importantly, bedtime cortisol levels decreased in the treatment group and increased in the placebo group. The average evening cortisol level at the end of the study was 4.9 (SD = 1.2) in the control group and 3.5 (SD = 0.96) in the treatment group. These results are consistent with the previously published study showing a correlation between elevated cortisol levels and stress-induced eating.[5]

DISCUSSION

The results of this study indicate that extracts of *M officinalis* and *P amurense* were well tolerated. There was a large placebo effect observed in the psychological measures; however, the non-subjective study variables, weight and salivary cortisol, showed beneficial effects of the treatment vs placebo. As a way of exploring the presumed mechanism of weight change (ie, reduced stress), correlations between changes in perceived stress and changes in weight over time were examined. There was no relationship between stress and weight change in the control group. In contrast, there was a positive correlation in the treatment group. Those whose stress levels decreased tended to maintain or reduce their weight ($r = .60$, $P < .01$). When negative mood was averaged across both time points, the weight maintainers had significantly lower average negative mood scores than weight gainers ($F_{1,16} = 6.5$, $P < .02$).

LIMITATIONS

This was a pilot scale study designed to determine whether there were any beneficial effects from the use of extracts of *M officinalis* and *P amurense* in this patient population before conducting a larger study. There was improvement in all of the psychological measures in both groups, resulting in no statistical differences between the groups. There was a disproportionate dropout rate in the placebo group. The duration of this study was 6 weeks, and the results may not be indicative of results from longer use of the supplement.

CONCLUSIONS

The extracts of *M officinalis* and *P amurense* were well tolerated with safety results comparable to placebo. Only 1 participant in the treatment group reported several side effects that the investigator judged to be possibly related to the treatment. There was a significant weight gain during the study for the placebo group—an average of 1.5 kg—and no significant weight gain for the treatment group. Participants in both the treatment and placebo groups had improved scores on a number of psychological measures during the study. There was a correlation between perceived stress and weight change. Nighttime cortisol levels in the treatment group decreased, but they increased in the control group, which supports previous findings that the extracts of *M officinalis* and *P amurense* reduce cortisol levels. The results of this pilot study indicate that the extracts of M officinalis and P amurense may reduce evening cortisol levels, systolic blood pressure, and possibly perceived stress, thereby helping participants maintain their body weight. The sample size was small, however, and there was higher attri-

tion in the control group. The results were in the expected direction and support the need for a larger clinical trial.

Disclosure

Dr Chambliss is chairman of the scientific advisory board for Next Pharmaceuticals, Inc, and is compensated by the company as a consultant.

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