

Relaxation During Weight Loss

Relieving Stress with an Herbal Combination

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The statistics of how overweight America is are well-known. However, Americans' stress levels, and their effects on sleep are important factors to consider in the obesity epidemic.

According to a National Institute for Occupational Safety and Health report, 40 percent of workers have reported that their jobs are very or extremely stressful; 26 percent of workers say they are "often or very often burned out or stressed by their work"; and job stress is associated more strongly with health complaints than financial or family problems.¹

A year 2000 Labor Day Gallup Poll on the Attitudes in the American Workplace² found that 80 percent of workers feel stress on their jobs, with nearly half of the respondents saying that they need help with managing their stress. Moreover, 25 percent of workers say they have felt like screaming or shouting because of stress. It appears that the American experience with stress is becoming progressively worse. This is an overweight nation that is gripped by stress.

As accounts of the adverse effects of stress on health continue to mount in the scientific literature, so do studies on adverse effects of sleep deficiency, which has been linked to obesity.

Researchers presented a study in November 2004 at the North American Association for the Study of Obesity, in partnership with the American Diabetes Association,³ reviewing the sleep patterns and obesity from earlier large nutrition studies conducted in the 1980s. The research team found that, of 6115 people, ages 32–59, those who slept only 2–4 hours a night were 73 percent more likely to be obese than normal (7–9 hours) sleepers; those who got 5 hours of sleep per night were 50 percent more

likely to be obese; those who slept for 6 hours were 23 percent more likely to be obese; and those who got 10 or more hours of sleep were 11 percent less likely to be obese.

Previous research has also found a link between lack of sleep and obesity. Sleeplessness was shown to activate an area in the hypothalamus that is involved in appetite regulation. {reference?} As the amount of sleep decreases, so does the amount of leptin produced in the brain. This may cause the body to crave more foods during the day.

Recent research has focused on what have been popularly termed "the stress hormones." During periods of increased stress, the hypothalamic–pituitary–adrenal axis becomes overactive and produces stress hormones, specifically cortisol. Normally, circulating levels of this hormone are highest in the morning and decrease throughout the day until they are lowest at bedtime. However, when a person is exposed to stressors, the cortisol levels increase. Elevated cortisol levels have been linked to weight gain in women and may explain the commonly recognized desire to eat during stressful periods.⁵

A Botanical Approach to Relaxing and Losing Weight

A new approach to weight loss is one that may have the pleasant side-effects of helping the dieter relax and experience a good night's sleep. And, in fact, a new class of weight-loss aids is being developed that focus on the interaction between stress and weight gain in the body, specifically by normalizing the cortisol levels in the body. Normalization of circulating cortisol levels should result in a reduction of the effects of stress on the body, a feeling of reduced anxiety and stress, and reduced cravings for comfort foods.

In response to this new understanding of weight gain, a dietary supplement consisting of proprietary extracts of two traditional Chinese herbs, magnolia (*Magnolia officinalis*) and phellodendron (*Phellodendron amurense*),* has been developed specifically for addressing stress and such stress-related conditions as elevated cortisol levels, sweet cravings, disrupted weight management, and poor quality of sleep.

The choice of the two botanicals for use in the proprietary

*The specific product discussed in this paper was developed by Next Pharmaceuticals, Inc., (www.nextpharmaceuticals.com) of Irvine, CA, which sells the supplement under the trade name Relora®. {Au: Please provide disclosure statement about Garrison having invented the product and being involved with it.}

extract was made after an extensive search for botanicals that showed good cortisol-lowering activity *in vitro*. Magnolia and phellodendron were chosen for their superior activity, as well as known long history of traditional use in Chinese medicine.

As is true for many botanical formulations, the full and complete mechanism of action of the magnolia/phellodendron combination is unknown. However, a significant body of research and clinical studies on some of the compounds in the formulation is consistent with the indications for which the supplement has demonstrated significant benefit. As with most natural products that are rich with more than one active compound, it is likely that the benefits derived from the magnolia/phellodendron extracts may be the result of more than a simple additive effect from the compounds that have been studied.

Chemistry and Preclinical Data

Conventional pharmaceutical medications used to treat anxiety and panic disorders include the benzodiazepine tranquilizers such as diazepam and oxazepam. These drugs act by enhancing inhibitory signals in the brain mediated by gamma-aminobutyric acid (GABA) and by activating one of its receptors, the GABA-A receptor. Other medications include serotonin agonists and serotonin reuptake inhibitors that boost serotonin concentrations. Agents that enhance the concentration of adenosine or activate the A1 receptors also cause a tranquilizing effect.

Clinical studies in China and Japan suggest that the Oriental herbal medicine *saiboku-to* relieves anxiety-related disorders such as anxiety neurosis.^{6,7} It has been demonstrated that the anxiolytic effect of *saiboku-to* results from the presence of magnolol and honokiol (from *Magnolia* spp. present in the *saiboku-to* formulation), two key compounds in proprietary formulation discussed here.⁸

These two compounds have also been shown to inhibit histamine release from rat mast cells.⁹ Benzodiazepines, including diazepam, bind to GABA-A receptors. Diazepam enhances the anxiolytic effect of *saiboku-to* (as a result of the presence of magnolol and honokiol) and flumazenil, a GABA-A antagonist, diminishes this anxiolytic effect.¹⁰

This suggests that the compounds in the magnolia/phellodendron formulation might exert their anxiolytic effect by acting as GABA-A receptor agonists. But more recent research suggests that the compounds in the formulation act by a different mechanism, possibly via an indirect cholinergic activity such as inhibition of histaminergic neurons linked to cholinergic neurons.¹⁰

An anxiolytic panel of receptors and transporter proteins associated with anxiety was developed in order to confirm the potential anxiolytic activity of the proprietary formulation. The results of these binding assays on two botanicals in the formulation are included in Table 1. The magnolia fraction demonstrated very significant binding to the adenosine A1, GABA-A (agonist), glutamate N-methyl-D-aspartate (NMDA), and serotonin transporter receptors.

This fraction also showed moderate binding to the adrenergic α_2 receptor and a negligible binding affinity for the other receptor sites of GABA-A (benzodiazepines and [³H]t-butylbicycloorthobenzoate [TBOB]) and glutamate (S)-2-amino-3-(3-

hydroxy-5-methyl-4-isoxazole) propionic acid (AMPA), indicating the relative specificity of the magnolia fraction and probability of minimal unwanted side-effects such as drowsiness and sedation caused by binding to other GABA-A receptor sites.

[[[Brian: Author would like Table 1 near here]]]]

The phellodendron fraction has a complementary binding profile to that of the magnolia fraction. It exhibits significant binding to the GABA-A receptor (agonist site), the α_2 adrenergic receptor, the serotonin transporter, and the adenosine A1 receptor. The phellodendron fraction has a negligible binding affinity for the other sites of GABA-A (benzodiazepines and TBOB), glutamate AMPA, NMDA, and other adrenergic receptors suggesting good specificity and a focused spectrum of action.

The unique combination of these two fractions in the proprietary composition takes advantage of a synergistic association resulting in complementary pharmacology. Concurrent binding affinities at four selective targets suggest a strong possibility of achieving a high level of response in a number of anxiety disorders. Because the chemical constituents in magnolia are different than those in phellodendron, it is anticipated that the synergy will provide therapeutic benefits at a lower dose than might be achieved by either fraction alone.

Clinical Data

Ongoing clinical data confirms the efficacy and safety of the magnolia /phellodendron formulation as a dietary supplement for supporting weight loss in times of stress. In the most recent placebo-controlled, double-blinded clinical study, the supplement or a matching placebo was administered at the dosage of 1 capsule (250 mg) three times daily for 6 weeks.

Participants in this study were healthy overweight, premenopausal female adults (a body-mass index [BMI] 25–34.9), between ages 20 and 50, who typically eat more in response to stressful situations, and who self-reported above the national mean for anxiety in women. These participants also led sedentary to moderately active lifestyles, with aerobic activity up to 4 days per week.

Additional objectives for determining safety were measured, including vital signs, adverse events, and specific laboratory markers of safety (serum glucose, liver/renal function, complete blood count with differential, hemoglobin and hematocrit values, and thyroid-stimulating hormone). **{Ok to delete the word thyroid before TSH definition?}**

Twenty-six (26) subjects completed the study, 16 in the supplement group and 10 in the placebo group. There was a significant weight gain during the study for the placebo group ($p < 0.89$) but not the treatment group ($p < 0.89$).

Compared to the placebo group, the supplement-treated group showed:

- A statistically greater reduction in anxiety (with a twofold greater decrease in the State-Trait Anxiety Inventory Anxiety Total Score)
- A significantly higher perceived stress/anxiety score (the high-

er the score, the better the patient is feeling)

- A significantly greater reduction in anxiety (with a greater than twofold improvement in the measure of General Feelings (Spielberger Trait Total Score).
- A greater increase in positive feelings and a greater decrease in negative feelings on the

Positive/Negative Anxiety measure (Positive and Negative Affect Scale scores).

In the treatment group there was also a nonsignificant trend for lowered average cortisol, and this was the result of the treatment effect on evening cortisol.

Amylase values tended to increase during the study in both groups, with statistical significance in the supplement-treated group ($p = 0.025$). In the treatment group, there was a significant decrease in sleep latency (by 11 minutes) compared to the placebo group. The magnolia/phellodendron supplement was well-tolerated, with no significant changes in laboratory values or vital signs during the study in either group.¹²

In an earlier placebo-controlled, double-blinded pilot study,[†] the supplement had been investigated for its safety and efficacy. Healthy overweight women between 20 and 50 (BMI 25–34.9) with the tendency to eat more in response to stressful situations (the same inclusion criteria of the above study) were included in this earlier study. The primary outcome measurements that were measured were stress, anxiety, mood, food intake, and salivary cortisol levels. Secondary outcome measures consisted of the results shown on comprehensive metabolic panel, a complete blood count with a differential analysis, blood pressure, heart rate, subjective adverse events, and physical adverse events.

A total of 28 subjects completed the study^{[[[fancy dagger]]]}—10 in the placebo group and 18 in the supplement-treated group. There was a significant weight gain during the study for the placebo group ($p < 0.01$) but no significant weight gain for the treatment group ($p < 0.89$). Seventy-five (75) percent of the placebo group gained 1 kg or more weight during the study versus 37 percent of the supplement group. Appetite for meals was similar in each group. Appetite for snacking was significantly lower in the supplement group at baseline and post-treatment.

There was a significant correlation between negative mood scores and weight gain in this earlier study.[†] Subjects who maintained their weight had significantly lower negative mood scores than subjects who gained weight during the study. In addition, there was a positive correlation between stress and weight change in the treated group and no correlation in the placebo group. Subjects who had reduced feelings of stress while taking the supplement tended to maintain or reduce their weight ($p < 0.01$). Salivary cortisol levels were measured 3 times a day at baseline and again for 3 days post-treatment. There was a trend toward lower average cortisol (the average of the 3 measure-

ments throughout the day) in the treated group mainly because of reductions at bedtime.

It was important that bedtime cortisol levels decreased in the supplement-treated group and increased in the placebo group. These results are consistent with the found correlation between weight maintenance and stress because elevated cortisol levels have been associated with stress-induced eating. The supplement was well-tolerated with no significant changes in laboratory values during the study in either group.

It is notable that there was a significant decrease in systolic blood pressure in the supplement group (an average reduction of 5 mmHg, $p = 0.04$) compared to an increase in the placebo group that could indicate a potential secondary benefit of therapy with this formulation. Overall, the supplement appeared to help subjects maintain their weight during the study, with a correlation between perceived stress and weight management. The mechanism of action for the herbal preparation appears to be via a reduction in cortisol levels that, in turn, causes a reduction in stress and helps subjects maintain body weight.^{[[[fancy dagger]]]}

Two home-use trials were conducted for preliminary clinical data on the Relora[®] magnolia/phellodendron supplement. In the first trial {reference?},¹¹ 50 stressed human subjects took the supplement for 2 weeks under a protocol developed by Dennis and Company (Nanuet, New York), experts in over-the-counter (OTC) drug home use trials. A post-trial analysis revealed that 82 percent of the subjects felt that the formulation helped control mild anxiety and alleviate associated symptoms, including poor sleep. (Of the 50 respondents, 48 percent said these claims were extremely believable," 34 percent said they were "somewhat believable," and 18 percent found them "not very/not at all believable.").

Relaxation was reported by 78 percent of the patients. (Of 50 respondents, 48 percent said that it was "highly effective," 30 percent said it was "moderately effective," and 22 percent said it was "not effective."). Seventy-four (74) percent of the subjects reported restful sleep. (Of 50 respondents, 48 percent said it was "highly effective" in producing restful sleep, 26 percent said it was "moderately effective," and 26 percent said it was "not effective.").

No significant side-effects were reported. Drowsiness was reported in 24 percent of the subjects. Ninety-four (94) percent of the subjects reported that the combination was gentle on the stomach.

In the second home-use trial {reference?},¹² 49 stressed human subjects who indicated they ate more sweets under stress were given the proprietary herbal compound for 2 weeks under a protocol developed by Target Research (Nanuet, New York; formerly Dennis and Company).

A post-trial analysis revealed that there was a dramatic and consistent decline (76 percent) in the type of high-calorie/high-fat foods subjects reported consuming before and after taking the supplement. The largest drops were seen in candy and sweets followed by salty snacks such as chips. Eighty-four (84) percent of the subjects reported more restful sleep. (Of the 49 respondents, 43 percent said they experienced "restful" sleep, 41 percent said they experienced "moderate" restful sleep, and 16

[†]Chambliss, W. A placebo controlled pilot clinical trial on the effect of Relora[®] capsules in the management of stress and eating behavior [unpublished data]. Irvine, CA: Next Pharmaceuticals, Inc., 2004.

percent said they experienced “not restful” sleep.) The vast majority of the subjects claimed that the supplement helped them relax without causing them to feel drowsy.

Safety and Contraindications

Toxicology

Three toxicology studies were conducted at Springborn Labs (Akron, Ohio): one on each extract in the compound, separately; and one utilizing the combination of the two extracts. An acute toxicity study in rats at 5000 mg/kg with 14-day observation revealed no untoward effects of the individual extracts or the combination except mild diarrhea and slight sedation in female rats. An LD₅₀ could not be established. No side-effects are expected at the recommended human dosage.

Contraindications

Pregnant or lactating women should not use the supplement.

Side-Effects

The magnolia/phellodendron supplement is generally well-tolerated. Some individuals experience mild drowsiness when they start taking it. This drowsiness usually dissipates within the first couple of days.

Drug Interactions

There are no known interactions between the supplement and prescription drugs. Although the effects of the herbal product on the hepatic cytochrome P-450 drug-metabolizing enzymes have not been studied, the action of *saiboku-to* on this system has been studied. *Saiboku-to*'s anxiolytic properties the result of magnolol and honokiol, two key compounds in the magnolia/phellodendron formulation. *Saiboku-to* does not affect the concentration of cytochrome P-450, the activities of the cytochrome P-450s related to diazepam metabolism, or the activities of CYP1A2 and CYP2C6 related to demethylation and hydroxylation of drugs.¹³ The compounds in the herbal formulation, magnolol and honokiol, exhibit anxiolytic and antihistamine properties. In addition, these compounds exhibit some central nervous system (CNS) depressant effects.^{14,15} Therefore, an additive effect is likely to occur if the supplement is taken in conjunction with any drugs in these classes.

Dosage

The adult dosage of the proprietary supplement is 750 mg daily in divided doses. Most individuals can take the herbal blend on an empty stomach. Food does not seem to affect the absorption of the active components, indicating that the supplement can also be taken with a meal. There is insufficient research to recommend the use of the formulation in children.

A Departure from Other Weight Loss Aids

Americans spend more than \$33 billion annually on weight-loss products and services, including so called “diet pills.”¹⁶ The development of weight-loss aids that work by relaxing the body

and reducing stress is a paradoxical direction from the diet pills of the past. Many of the “old school” weight-loss aids contain CNS stimulants, such as caffeine and the now Food and Drug Administration–banned ephedrine. The Mayo Clinic (Rochester, New York) and individual practitioners are now beginning to discourage the use of caffeine for weight loss, and debunking the myth that caffeine helps keep the body slim.¹⁷ As caffeine is a regularly ingested substance, it is helpful to review its effect on the body and weight loss for comparison.

Effects of Caffeine

Caffeine is known to elevate stress hormones, such as cortisol, epinephrine, and norepinephrine. An implication of new research demonstrating the connection between weight gain and elevated stress hormones, may be that caffeine might promote weight gain.^{18–20} In addition, CNS stimulants, such as caffeine, lead to increased stress and overeating.^{21–24}

Caffeine also has been found to worsen insulin resistance. It does this by impairing glucose and insulin homeostasis as part of the stress response.^{25,26} Additionally, caffeine stimulates the appetite over the long term, after a short period when it may decrease the appetite.^{3,27} Caffeine also interferes with GABA metabolism and coffee drinking is known to increase serum cholesterol levels.^{28–33}

Conclusions

Before the invention of the lightbulb, people slept an average of 10 hours a night. Today, humans are not only sleep-deprived; they are also stressed and overweight. In the past—and even to the current day—diet pills were made to speed up the metabolism to promote weight loss. What if widespread unhappiness with jobs and stressful lives, and the relationship of unhappiness to the human body and health were all linked, and the human species is worrying itself fat? Perhaps this new class of diet aids can provide much needed support to stressed-out, poorly rested people who are to trying to lose weight and lead more relaxed and healthful lives. □

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Table 1. Proprietary Magnolia/Phellodendron Formulation's Receptor-Binding Assays

Assay	Sample #	
	NPS00033	NPS00039
5-HT1, serotonin		23.12
5-HT2A, serotonin		
5-HT3, serotonin		
Adenosine A1	67.82	75.94
Adrenergic α1		-116.7
Adrenergic α2	90.34	49.69
Adrenergic α2		
Adrenergic αinesp		
CCKB, cholecystokinin		
Corticotropin rf		-52.03
D2, dopamine		
Displacement of NE		
Dopamine transporter		
GABA BDZ site	-25.77	8.9
GABA TBOB	-6.24	
GABA-A agonist	95.91	77.73
Glutamate AMPA		16.39
Glutamate NMDA	18.97	76.81
Histamine H3		
NE transporter	29.7	27.77
Peripheral benzodiazepine	7.22	
Serotonin nonselective	26.87	4.95
Serotonin transporter	90.08	62.4

GABA = gamma-aminobutyric acid; TBOB = [³H]-t-butylbicycloorthobenzoate; NMDA = N-methyl-D-aspartate; AMPA = (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazole) propionic acid.