

## The Safety and Efficacy of a Dietary Herbal Supplement and Gallic Acid for Weight Loss

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**ABSTRACT** The objective of this study was to test the safety and efficacy of NT, a dietary herbal supplement made from rhubarb, ginger, astragalus, red sage, and turmeric, combined with gallic acid (GA) to reduce food intake and cause weight loss. A total of 105 healthy subjects, 18–60 years old with a body mass index of 25–35 kg/m<sup>2</sup> and on no chronic medication, were randomized to a 300 mg/1.2 g NT-GA combination, a 600 mg/2.4 mg NT-GA combination, or placebo in three divided doses daily for 24 weeks. Food intake was measured at baseline and 2 weeks, and safety parameters were followed regularly. Pharmacokinetic studies of a 200 mg/800 mg NT-GA combination and 800 mg GA alone were performed with and without food. There was no dose-related weight loss or reduction in food intake at the 8-week analysis, and the study was terminated early. Pharmacokinetic studies showed plasma levels of GA did not increase above 10  $\mu$ M and were not dose-related. The NT-GA at all concentrations was well tolerated, but was ineffective in causing weight loss or in suppressing food intake. Pharmacokinetics suggested that GA plasma levels were limited by oral absorption, and may be the reason for lack of efficacy.

**KEY WORDS:** • *astragalus* • *gallic acid* • *ginger* • *human* • *red sage* • *rhubarb* • *turmeric*

### BACKGROUND

NT IS AN HERBAL SUPPLEMENT derived from a water extract of 40% rhubarb root and stem (radix and rhizoma *Rheum*), 13.3% astragalus root (radix *Astragalus*), 13.3% red sage root (radix *Salvia miltiorrhizae*), 26–27% turmeric (rhizoma *Curcuma longa*), and 6–7% dried ginger (rhizoma *Zingiberis officinalis*). NT caused weight loss and reduced weight gain in rodents in China,<sup>1</sup> and its ability to suppress weight gain in rodents was confirmed by York *et al.*<sup>2</sup> in the United States.

A pilot study testing the efficacy and safety of NT to induce weight loss in humans produced diarrhea as a result of sennosides, herbal laxatives present in the NT, but was otherwise well tolerated.<sup>3</sup> NT was demonstrated to also contain gallic acid (GA), a compound known to give weight loss and reduce food intake in rodents when given either orally or parenterally.<sup>4</sup> Therefore, in an effort to reduce the side effects of NT and preserve weight loss efficacy, a mixture of NT (20% by weight) with herbal GA derived from gall

nuts (80% by weight) was tested for safety and efficacy in treating human obesity.

GA is generally recognized as safe in the form of galotannins by the Food and Drug Administration and has been used as an antioxidant in food. Toxicology studies in rodents show that the no observed adverse effect level (NOAEL) is 120 mg/kg, a dose equivalent to 2.9 g in a 70-kg man.<sup>5</sup> GA is available from herbal sources that can be used to increase the concentration in NT. The human equivalent amount of GA in the low dose of NT shown to be effective for weight loss in rodents is 1.2 g/day, less than half the NOAEL.<sup>6</sup>

An 8-week pilot study was performed at the Pennington Center (Baton Rouge, LA) in eight healthy females with a body mass index (BMI) between 25 and 35 kg/m<sup>2</sup> on no regular medications except birth control or hormone replacement therapy. Subjects were randomized to two placebo capsules three times a day or two capsules each containing 200 mg of GA from an herbal source and 50 mg of crude NT extract given three times a day, for a total of 1.2 g of GA and 300 mg of crude NT extract/day. This dose of GA was less than 50% of the NOAEL, and the amount of NT was only 5% of the dose shown to give loose stools. Weight loss in the NT-GA group was 3% of body weight compared to 1.8% in the placebo group ( $P = .38$ ). Compliance by pill count was >98%, and there were no significant

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changes in blood pressure, pulse, complete blood counts, or chemistry panel values throughout the trial. There were no adverse events felt to be related to the treatment, and there were no changes in the physical examinations or electrocardiograms.

Results of the pilot study were used to power a 6-month clinical trial testing the safety and efficacy of two doses of the NT-GA mixture. One dose was the same as that used in the pilot trial, *i.e.*, 1.2 g of GA/day, and the second dose contained 2.4 g of GA/day, below the 2.9 g/day determined to be the NOAEL calculated from the metabolic mass equation using the data from rats.<sup>6</sup>

## SUBJECTS AND METHODS

### Main study design

One hundred five healthy volunteers between the ages of 18 and 60 years of age with a BMI between 25 and 35 kg/m<sup>2</sup> and on no chronic medication other than oral contraceptives or hormone replacement therapy participated in this 24-week study. Subjects had height, weight, and blood pressure measured, pulse taken, and a complete blood count (hemoglobin, hematocrit, mean corpuscular volume, platelets, white blood cell count, neutrophil number, and eosinophil number) and chemistry panel (creatinine, uric acid, potassium, glucose, albumin, calcium, magnesium, iron, creatine phosphokinase, alanine leucine transaminase, alkaline phosphatase, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) done at screening. A registered dietitian at baseline instructed subjects in a diet 700 kcal/day below weight maintenance requirements based on the World Health Organization formula.<sup>7</sup> At baseline an electrocardiogram, medical history, and physical examination were done, and women had a pregnancy test performed. Subjects were randomized to two doses of an NT mixture (20% NT and 80% GA) or placebo supplied by Deseret Laboratories International (St. George, UT). The NT enriched with GA was given at either 1.2 g of GA and 300 mg of NT/day or at 2.4 g of GA and 600 mg

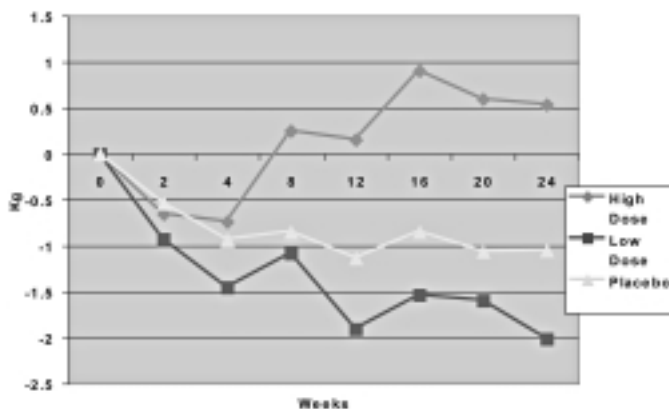


FIG. 1. Weight loss (in kg) at the end of the study (24 weeks).

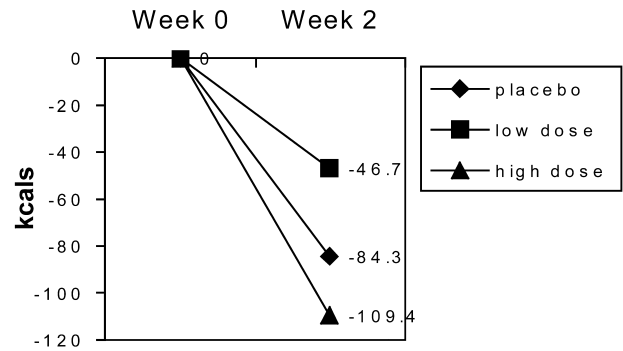


FIG. 2. Change in food intake (in kcal) from baseline to week 2 by group.

of NT/day versus placebo in a 1:1:1 ratio. Capsules contained 200 mg of GA and 50 mg of NT or placebo. Subjects took two capsules three times a day. On each visit (weeks 0, 2, 4, 8, 12, 16, 20, and 24) subjects were weighed, had blood pressure measured, pulse taken, and medications dispensed, and questioned about any adverse events, and medication bottles were returned. The physical exam, complete blood count, chemistry panel, pregnancy test, and electrocardiogram were repeated on week 24 at the end of the study.

### Food intake

Subjects had food intake evaluated with a universal eating monitor at screening and at week 2 of the study. Subjects visited the food intake laboratory after an overnight fast during which only water was allowed. Subjects completed Visual Analogue Scales (VAS) of appetite and a questionnaire about factors that might affect taste such as colds or allergies. They were then given two pills to swallow, and the VAS was repeated after 1 hour. An hour after receiving the pills the subjects were given a meal of sandwich quarters, chips, and cookies larger than they could reasonably eat, and they were allowed to eat as much or as little as they wished for 20 minutes. At completion of the meal subjects completed the VAS again. Subjects were given placebo on the first visit and the treatment to which they were randomized on week 2.

### Pharmacokinetic substudy

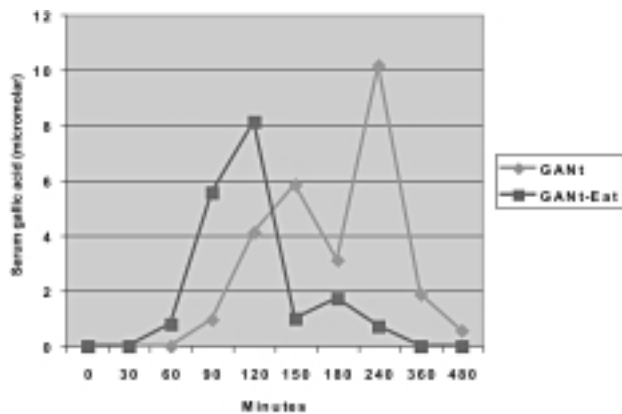
Five healthy men between the ages of 18 and 60 years with a BMI between 20 and 35 kg/m<sup>2</sup> were enrolled. Subjects took no regular medication and were not lactose intolerant. Subjects had a medical history, physical examination, and chemistry panel performed at screening. All subjects received a GA-free diet of white bread, cheese, butter, and water or milk for the day prior to and the day of each pharmacokinetic test lasting through the end of a 24-hour urine collection.

The first two subjects had two pharmacokinetic tests 1 week apart. The first subject had one test with GA from gall

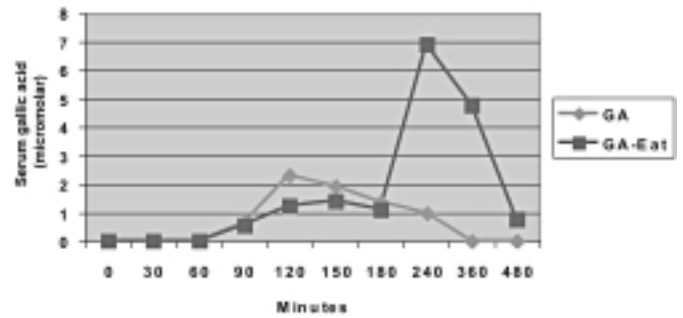
nut extract 800 mg after an overnight fast, and the other test was with GA from gall nut extract 800 mg along with a 570 kcal meal consisting of a grilled cheese sandwich and a glass of milk. The second subject had one test with gall nut extract 800 mg combined with NT 200 mg after an overnight fast, and the other test was with GA from gall nut extract 800 mg combined with NT 200 mg along with the same 570 kcal meal. The mixture of 800 mg of GA from gallnut extract and 200 mg of NT was the same as the high dose of the NT-GA mixture used in the trial. Subjects reported fasting on the morning of the test and took test medication orally. Ten-milliliter blood samples were collected at times 0, 30, 60, 90, 120, 150, 180, 240, 360, and 480 minutes. The blood was collected in heparinized tubes and centrifuged, and plasma was separated and frozen until analyzed on high-pressure liquid chromatography for GA and GA metabolites. The second two subjects had one test day after an overnight fast with GA from gall nut extract 800 mg without a meal. The fifth subject had one test day after an overnight fast in which he let 800 mg of GA from gall nut extract contained in hard candy dissolve in his mouth. All subjects emptied their bladders at time 0, and an aliquot of the urine was frozen for later analysis. All urine was collected for the 24 hours following the GA ingestion. The urine volume was measured, and an aliquot was frozen for later measurement of GA and GA metabolites.

### Statistics

The study was designed to extend over 24 weeks with interim analysis at 8 weeks. Thus, the study was powered for two endpoints, the interim endpoint at 8 weeks and the 24-week endpoint. The first power calculation for the 8-week time point was based on a standard deviation of 4 kg, a value derived from Pennington weight loss studies at 8 weeks. Since the expected difference between the 2.4 g GA group and placebo was 3 kg at 8 weeks based on the pilot study, there was an 80% power to detect this difference at 8 weeks, with 29 subjects finishing in each group at  $P < .05$ . Allow-



**FIG. 3.** Serum levels of GA after GA (800 mg)-NT (200 mg) with and without food in one subject on two occasions.



**FIG. 4.** Serum levels of GA after GA (800 mg) with and without food in one subject on two occasions.

ing for a 20% dropout rate, one needed to enroll 35 subjects per arm.

The second power calculation was for the 24-week time point and was based on a standard deviation of 6.5 kg, a value derived from the Pennington Center weight loss studies at 24 weeks. Since the expected difference between the 2.4 g GA group and placebo was 5 kg at 24 weeks based on the pilot study, there was an 80% power to detect this difference at 24 weeks with 28 subjects finishing in each group at  $P < .05$ . Allowing for a 20% dropout rate, one needed to enroll 35 subjects per arm.

Repeated-measures analysis of variance was used to compare weight loss in the NT-GA and placebo groups. The interim analysis was performed at 8 weeks and a final analysis at 24 weeks. The primary study endpoint was body weight. Secondary endpoints were food intake and safety measures (laboratory, adverse events, and electrocardiograms). The study was powered to detect a 3 kg difference at 8 weeks and a 5 kg difference at 24 weeks at 80% power with an  $\alpha$  of .05.

## RESULTS

### Efficacy

**Weight loss.** The planned interim analysis was performed at 8 weeks. Baseline weights in the placebo, low-dose, and high-dose groups were  $83.3 \pm 2.05$  kg (SEM),  $84.1 \pm 2.53$  kg, and  $82 \pm 2.18$  kg, respectively. The placebo group behaved as expected with an average ( $\pm$  SEM) weight loss of 0.7% body weight ( $0.6 \pm 0.42$  kg). Subjects receiving the low-dose NT-GA mixture (1.2 g of NT/300 mg of GA) lost 1.2% body weight ( $2.6 \pm 1.3$  kg), which was statistically different than placebo ( $P < .05$ ). Subjects on the high-dose NT-GA mixture (2.4 g of NT/600 mg of GA) lost 0.6% body weight ( $0.46 \pm 0.74$  kg), an amount that was not different from placebo. The trial was terminated when the interim analysis showed no evidence of efficacy. Thus, the number of subjects completing the trial was fewer than anticipated. At the end of 24 weeks, there were 19 subjects in the high-dose group, 20 subjects in the low-dose group, and 25 subjects in the placebo group. The final weight loss at 24 weeks was  $1.05 \pm 0.54$  (SEM) kg in the placebo group and  $2.01 \pm$

1.18 kg in the low-dose group but a gain of 0.54 + 0.79 kg in the high-dose group. The difference between the high- and low-dose groups was statistically significant ( $P = .044$ ), but weight loss in the NT-GA groups was not significantly better than placebo (Fig. 1).

F1

**Food intake.** Food intake was measured in the eating laboratory at weeks 0 and 2. One-way analysis of variance indicated that the three groups' food intake (in kcal) did not differ significantly at week 0 [ $F(2, 102) = 1.37, P = .26$ ]. Dependent  $t$  tests indicated that food intake (in kcal) decreased significantly from week 0 to week 2 for the high-dose group only [ $t(32) = 2.33, P < .05$ ]. Nevertheless, independent-samples  $t$  tests indicated that the food intake difference scores (food intake at week 2 minus week 0) did not differ between the placebo and low-dose group [ $t(70) = -0.39, P = .70$ ] or the placebo and high-dose group [ $t(67) = 67, P = .73$ ]. The change in food intake from week 0 to week 2 by group is illustrated in Figure 2.

F2

### Safety

**Blood pressure and pulse rate.** Systolic blood pressure rose 1.9 + 2.3 (SD) mm Hg in the placebo group and 1.7 + 2.1 mm Hg in the high-dose group but fell 1 + 1.8 mm Hg in the low-dose group. Diastolic blood pressure rose 1.9 + 1.5 mm Hg in the high-dose group, 0.43 + 1.9 mm Hg in the low-dose group, and 0.8 + 1.3 in the placebo group. The pulse rate rose 2.6 + 2.5 bpm in the high-dose group, 3.2 + 2.4 bpm in the low-dose group, and 1.0 + 1.9 in the placebo group. None of these differences was statistically significant.

**Complete blood counts, chemistry panel, liver function, and lipids.** Hemoglobin and hematocrit fell significantly in the high dose NT-GA group compared to the placebo group [ $-0.51 + 0.21$  vs.  $-0.02 + 0.12$  g (SEM) and  $-1.9 + 0.6$  vs.  $-0.62 + 0.65\%$ , respectively ( $P < .05$ )]. Uric acid dropped more in the high-dose group than in the low-dose or placebo groups [ $-0.71 + 0.24$  vs.  $-0.05 + 0.12$  vs.  $-0.16 + 0.12$  mg/dL, respectively ( $P < .05$ )]. There were no other dose-related changes in laboratory testing. Labora-

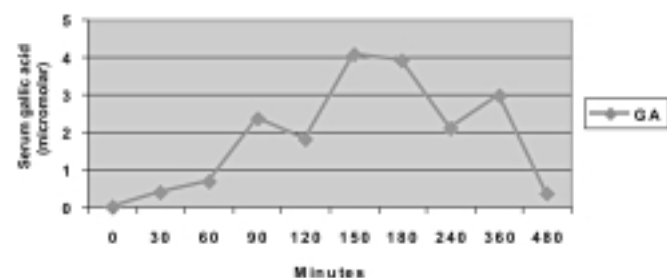


FIG. 5. Serum levels of GA in three subjects after oral ingestion of 800 mg.

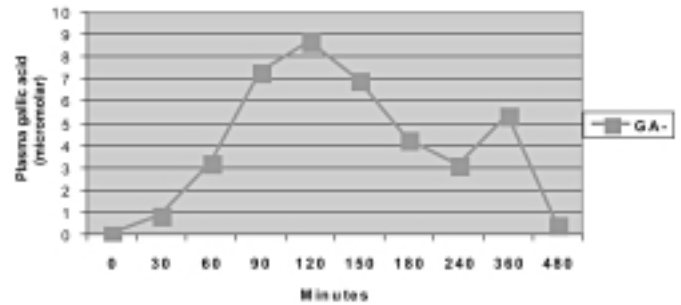


FIG. 6. Serum levels of GA in one subject after letting candy with 800 mg of GA dissolve in the mouth, fasting.

tory values were fluctuations within the normal range, and none of the changes was clinically significant.

**Compliance.** Pill counts showed that subjects in the low-dose group took 94.8 + 0.8%, placebo group took 93 + 0.8%, and high-dose group took 92.2 + 1.5% of the pills prescribed. These compliance numbers did not differ between groups.

**Pharmacokinetics.** The subject who took NT-GA (200 mg/800 mg) on two occasions, once fasting and once with food, had a peak GA concentration in the plasma of 10  $\mu\text{M}$  without food at 4 hours, and a peak plasma concentration of 8  $\mu\text{M}$  with food at 2 hours (Fig. 3). The subject who took GA 800 mg on two occasions, once fasting and once with food, had a peak GA concentration in plasma of 2  $\mu\text{M}$  without food at 2 hours and a peak plasma concentration of 7  $\mu\text{M}$  with food at 4 hours (Fig. 4). The three subjects who had 800 mg of GA orally when fasting had a peak plasma concentration of GA in the plasma of 4  $\mu\text{M}$  at 2.5–3 hours (Fig. 5). The one subject who let candy containing 800 mg of GA dissolve in his mouth fasting had a peak plasma concentration of GA of 9  $\mu\text{M}$  at 2 hours (Fig. 6). Measurement of GA in the urine revealed that the capsules of GA with or without NT had about 6% absorption. Eating increased absorption to the 9–12% range. Allowing for complete dissolution and allowing for possible transmucosal absorption using candy containing GA dissolved in the mouth increased absorption further to 19% (Fig. 7).

F3

F4

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F6

F7

## DISCUSSION

When GA was fed to rats at levels of 2%, 4%, 5%, 6%, 8%, and 10% of diet, food intake was depressed, and there were no deaths up to 5% of the diet. At 5% of diet GA depressed food intake by 50% with a similar reduction in body weight compared to control.<sup>8</sup> There was a marked increase in hepatic fat in rats fed a diet with 5% GA (36% vs. 7% of dry weight), which was not seen with similar levels of tannic acid.<sup>9</sup> Fecal protein excretion increased with feeding of the diet supplemented with tannic acid, but was not significantly different from control with diets supplemented with

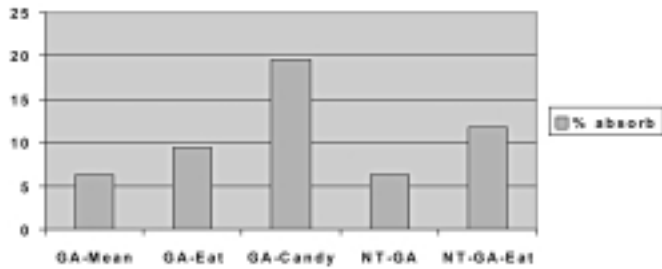


FIG. 7. Percent absorption of GA from the gastrointestinal tract and the effect of food on absorption.

GA.<sup>10</sup> GA was also shown to decrease food intake when infused intraperitoneally as a 2% solution. Thus, the mechanism by which GA decreases food intake involves more than taste aversion or gastrointestinal factors.<sup>4</sup>

These studies with GA, along with evidence that NT contained GA, encouraged us to explore the use of herbal GA combined with NT for the treatment of obesity in humans. The NOAEL in rodents is 120 mg/kg, a dose equivalent to 2.9 g/day in a 70-kg man using the metabolic mass equation.<sup>5,6</sup> The daily doses of GA used in this study were up to 2.4 g, well below the NOAEL in these obese subjects. The doses of NT used in this study did not exceed 600 mg, 1/10<sup>th</sup> of the dose that gave loose stools in a clinical trial of NT.

The NT-GA mixture was well tolerated, and loose stools were not a problem. Disappointingly, the combination did not give weight loss. In fact, the high dose gave less weight loss than the placebo. This was surprising in view of the experience in rodents in which food intake was suppressed. A human pharmacokinetic study of GA by Shahrzad *et al.*<sup>11</sup> demonstrated that 40% of a 50 mg dose of GA was absorbed and achieved a peak serum concentration between 1.8 and 2.1  $\mu\text{M}$  at 70 minutes. We developed a high-pressure liquid chromatography method to measure GA and did pharmacokinetic studies with the high dose of NT-GA (200 g of NT/800 mg of GA) and with the GA it contained. Only 6% was absorbed, giving a peak serum concentration of 4  $\mu\text{M}$ . Food appeared to increase absorption, and letting hard candy containing 800 mg of GA dissolve in the mouth further increased absorption. Even in the best of circumstances the absorption never exceeded 19%, and the plasma levels never exceeded 10  $\mu\text{M}$ . This suggests, but does not prove, that GA absorption is limited in humans by an active transport system that becomes saturated far below the levels needed to get levels of GA into the plasma that are adequate to suppress food intake.

Unfortunately, the NT-GA pilot data that looked so encouraging for weight loss appear to have been misleading because of the small numbers of subjects, which precluded obtaining a statistically significant result. The information generated by this trial is still important to report. The animal data were very encouraging that GA would be effective and safe for weight loss, and it is likely that someone else would have explored this possibility. This trial gives evidence that GA will not be an effective oral supplement for the treatment of human obesity.

## ACKNOWLEDGMENTS

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**ROBERTS**

**AU1  
update?**