Garcinia cambogia (Hydroxycitric Acid) as a Potential Antiobesity Agent

A Randomized Controlled Trial

Steven B. Heymsfield, MD; David B. Allison, PhD; Joseph R. Vasselli, PhD; Angelo Pietrobelli, MD; Debra Greenfield, MS, RD; Christopher Nunez, MEd

Context.—Hydroxycitric acid, the active ingredient in the herbal compound *Garcinia cambogia*, competitively inhibits the extramitochondrial enzyme adenosine triphosphate–citrate (pro-3S)-lyase. As a citrate cleavage enzyme that may play an essential role in de novo lipogenesis inhibition, *G cambogia* is claimed to lower body weight and reduce fat mass in humans.

Objective.—To evaluate the efficacy of *G cambogia* for body weight and fat mass loss in overweight human subjects.

Design.—Twelve-week randomized, double-blind, placebo-controlled trial.

Setting.—Outpatient weight control research unit.

Participants.—Overweight men and women subjects (mean body mass index [weight in kilograms divided by the square of height in meters], approximately 32 kg/m^2).

Intervention.—Subjects were randomized to receive either active herbal compound (1500 mg of hydroxycitric acid per day) or placebo, and both groups were prescribed a high-fiber, low-energy diet. The treatment period was 12 weeks. Body weight was evaluated every other week and fat mass was measured at weeks 0 and 12.

Main Outcome Measures.—Body weight change and fat mass change.

Results.—A total of 135 subjects were randomized to either active hydroxycitric acid (n = 66) or placebo (n = 69); 42 (64%) in the active hydroxycitric acid group and 42 (61%) in the placebo group completed 12 weeks of treatment (P = .74). Patients in both groups lost a significant amount of weight during the 12-week treatment period ($P < .001$); however, between-group weight loss differences were not statistically significant (mean [SD], 3.2 [3.3] kg vs 4.1 [3.9] kg; P = .14). There were no significant differences in estimated percentage of body fat mass loss between treatment groups, and the fraction of subject weight loss as fat was not influenced by treatment group.

Conclusions.—*Garcinia cambogia* failed to produce significant weight loss and fat mass loss beyond that observed with placebo.

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EXCESSIVE ADIPOSITY and its concomitant health risks are among the most common conditions managed by health care practitioners. The limited long-term effectiveness of conventional weight management, including behavioral therapy,[1] is the impetus of major efforts aimed at developing alternative pharmacologic[2] and surgical weight reduction treatment strategies.[3] A rapidly growing therapeutic area, and one widely embraced by the general public, is the use of herbal weight loss products.

An herb-derived compound, hydroxycitric acid, is now incorporated into many commercial weight loss products. Obtained from extracts of related plants native to India, mainly *Garcinia cambogia* and *Garcinia indica*, hydroxycitric acid was first identified by Watson and Lowenstein[4,5] in the late 1960s as a potent competitive inhibitor of the extramitochondrial enzyme adenosine triphosphate–citrate (*pro-3*S)-lyase. These investigators and others subsequently demonstrated both in vitro and in vivo that hydroxycitric acid in animals not only inhibited the actions of citrate cleavage enzyme and suppressed de novo fatty acid synthesis,[6] but also increased rates of hepatic glycogen synthesis,[7] suppressed food intake,[8] and decreased body weight gain.[9]

Although hydroxycitric acid appears to be a promising experimental weight control agent, studies in humans are limited and results have been contradictory[10-14] (also R. Ramos, J. Flores Saenz, F. Alarcon, unpublished data, 1996, and G. Kaats, D. Pullin, L. Parker, S. Keith, unpublished data, 1996). Supporting evidence of human hydroxycitric acid efficacy for weight control is based largely on studies with small sample sizes,[11,12] studies that failed to include a placebo-treated group,[10] and use of inaccurate measures of body lipid change.[12] Although hydroxycitric acid effectiveness remains unclear, at least 14 separate hydroxycitric acid–containing products are presently sold over-the-counter to consumers.[15] This investigation was designed to overcome limitations of earlier studies and examine the effectiveness of hydroxycitric acid for weight loss and fat mass reduction in a rigorous controlled trial.

METHODS

Protocol

We tested 2 primary hypotheses in a randomized, double-blind, placebo-controlled trial: (1) *G cambogia* produces a greater reduction in body weight than placebo, and (2) *G cambogia* produces a greater reduction in total body fat mass than placebo. Advertisements were placed in local newspapers, and over-

weight subjects who responded and met entry criteria during a telephone screening interview were scheduled for a baseline visit. The evaluation included a physical examination, electrocardiogram, and screening blood studies. Subjects meeting entry criteria were seen within 2 weeks for randomization at treatment week 0. Subjects were assigned to placebo or active compound with equal probability through a random number generator.

The protocol with active herbal compound included *G cambogia* extract (50% hydroxycitric acid by chemical analysis), taken 3 times daily as two 500-mg caplets 30 minutes before meal ingestion. Total daily dose was *G cambogia* extract, 3000 mg, and hydroxycitric acid, 1500 mg. Placebo-treated subjects followed an identical protocol in which active compound was replaced with inert ingredients. Subjects taking active compound or placebo were provided a high-fiber, 5040-kJ/d diet plan, with 20%, 50%, and 30% of energy as fat, carbohydrate, and protein, respectively. The recommended daily food provision was divided into 3 meals with an evening snack. Subjects were asked to maintain a stable physical activity level and return for evaluation every 2 weeks for a total treatment interval of 12 weeks. Body weight was measured at each visit, and clinical information, including potential herb or weight loss adverse effects, was obtained. Biweekly pill counts and diaries were used to check patient medication compliance. Diet compliance was not quantitatively monitored during the study.

The study was approved by the institutional review board of St Luke's–Roosevelt Hospital Center, New York, NY, and all subjects gave written consent prior to participation.

Subjects

Subjects were overweight but otherwise healthy adults aged 18 to 65 years who had a body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) of more than 27 kg/m^{2} and at most 38 kg/m^{2}. Subjects were excluded if they were pregnant, had any clinically significant medical condition, were taking prescription medications or appetite suppressants on a regular basis, had a history of alcohol or other drug abuse, were allergic to any of the study products, or had dieted with weight loss in the past 6 months.

Body Composition

Body weight and height were measured to the nearest 0.1 kg and 0.5 cm using a digital scale (Weight Tronix, New York, NY) and stadiometer (Holtain, Crosswell, Wales), respectively.

Total body fat mass was measured at baseline and at the 12-week visit using several different procedures.

A pencil-beam dual-energy x-ray absorptiometry (DXA) scanner (Lunar DPX, Madison, Wis) was used to estimate total body fat mass. Subjects completed the slow-mode whole body scan and fat mass estimates were provided by Lunar, Version 3.6g, software.[16] The technical error of DXA percentage fat mass estimates in our laboratory is 3.1%.[17] The remaining body fat mass measurement methods used in our laboratory for this study included underwater weighing,[18] skinfold thicknesses,[19] and bioimpedance analysis.[20]

Statistical Analysis

Based on previous research,[1] we estimated that a study that included at least 30 completed subjects in each of 2 groups would have more than 80% power at the 2-tailed α level of .05 to detect any significant differences in body weight.

The 2 study hypotheses were tested in separate sets of statistical analyses. Statistical models were used in which the outcome variable, either loss of body weight or percentage of fat mass, was set as dependent variable and assigned treatment and other covariates were set as independent variables in an intent-to-treat analysis.[21] Within the intent-to-treat analysis, missing data due to measurement failure or subject dropout were imputed by carrying the last observation forward (LOCF).[22] The baseline value of the dependent variable (ie, initial body weight or percentage of fat mass) served as a potential independent variable in each analysis. Patient age and sex also served as additional independent variables. All analyses were conducted at the 2-tailed α level of .05.

For each of the 2 dependent variables, a set of secondary analyses were conducted, including (1) evaluation of completers only; (2) imputation of all missing data with a regression procedure rather than the LOCF; (3) imputation of missing data using the EM[23] algorithm rather than the LOCF; (4) use of weight loss slopes as outcomes[24] rather than the

simple baseline to final measurement change when more than 2 time points for weight were available; (5) performance of a full repeated-measures analysis of variance using all time points; and (6) performance of a multivariate analysis of covariance using all time points simultaneously in the statistical model. In no case did any of these secondary sensitivity analyses lead to different conclusions than the primary LOCF intent-to-treat analysis. We therefore report only the results of the primary intent-to-treat analysis.

At baseline, DXA readings were unavailable for several subjects who had technically poor scans or who were evaluated during a brief period in which the DXA system was undergoing repair. However, each of these subjects had 1 or more measurements of fat mass taken with the other techniques mentioned herein and summarized in earlier articles.[16-20] Estimates of total body fat mass for these subjects by DXA were inferred using single imputation plus random error models based on multiple regression analysis of all other available measurements of fat mass for that subject, as described by Graham et al.[25] Similarly, several subjects completed the entire course of treatment and received some measurement of body fat mass after treatment but not by DXA. For these subjects, estimates of total body fat mass by DXA also were imputed using the same statistical methods and the other available measurements of body fat mass.

The purported fat-mobilizing properties of hydroxycitric acid were evaluated by computing the slope of change in fat mass vs change in body weight for the 2 treatment groups. Assuming approximately a zero intercept for this relation, the anticipated regression line slopes should approach 0.7 to 0.8, the generally acknowledged fraction of weight loss as fat mass in obesity trials.[26] Promotion of fat mass loss by active hydroxycitric acid would be associated with an increased fraction of weight loss as fat mass.

Group results are expressed as mean (SD) in text and tables. Data were analyzed using the statistical programs
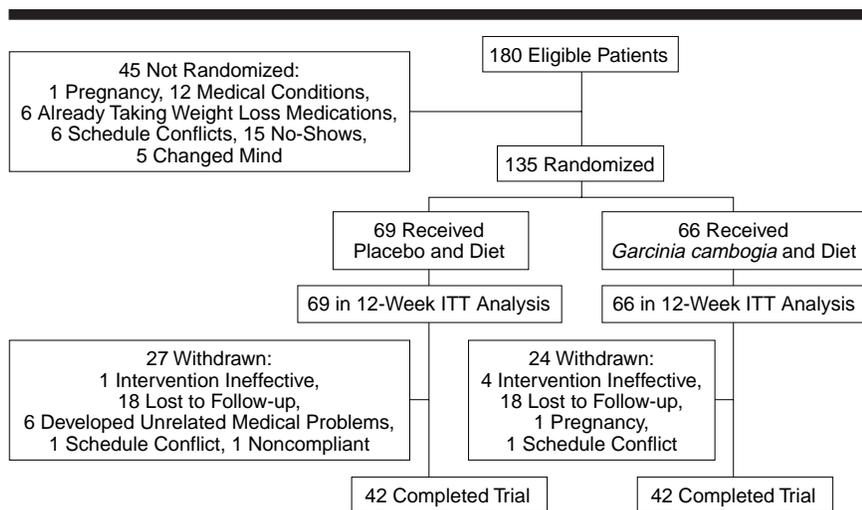
Table 1.—Baseline Subject Characteristics*

Group	No. of Patients	Age, y	Weight, kg	BMI, kg/m²†	Total Body Fat Mass, %
Treatment					
Men	5	43.1 (2.8)	100.8 (11.0)	33.0 (3.7)	28.4 (2.6)
Women	61	38.2 (7.8)	82.9 (8.8)	31.1 (2.7)	41.9 (7.3)
Total	**66**	38.6 (7.7)	83.8 (10.1)	31.2 (2.8)	41.1 (7.8)
Placebo					
Men	14	40.5 (5.5)	101.7 (11.8)	32.3 (2.5)	36.6 (5.9)
Women	55	39.6 (7.6)	84.8 (10.9)	31.4 (3.2)	43.8 (4.2)
Total	**69**	39.4 (7.2)	88.2 (13.0)	31.9 (3.1)	42.0 (5.6)

*Data (except number of patients) are presented as group mean (SD).
†BMI indicates body mass index, defined as weight in kilograms divided by the square of height in meters.

Figure 1.—Study CONSORT flow diagram. ITT indicates intent-to-treat.

Figure 2.—Weight-change curves for 2 study groups. Results are plotted for group means (±95% confidence limits) for 69 subjects in the placebo group and 66 subjects in the treatment group. Data are from last-observation-carried-forward intent-to-treat analysis.

SPSSWIN, Version 7.5, and SPSSMVA, Version 7.5 (SPSS Inc, Chicago, Ill).

RESULTS

Baseline Characteristics

At baseline, 180 moderately overweight subjects were screened and, of those, 135 were randomized to placebo and active compound (Table 1 and Figure 1). There were 69 subjects (BMI, 31.9 [3.1] kg/m²) in the placebo-treated group (14 men and 55 women) and 66 subjects (BMI, 31.3 [2.8] kg/m²) in the *G cambogia*–treated group (5 men and 61 women).

Of the 69 placebo-treated subjects, 42 (61%) completed the 12-week protocol. The reasons for subject withdrawal (27 cases) are summarized in Figure 1. Of the 66 subjects randomized to active compound, 42 (64%) completed the 12 weeks of treatment. The reasons for subject withdrawal from this group (24 cases) are also summarized in Figure 1. There were no significant differences in age, body weight, or BMI between subjects who withdrew from the study and those who completed the 12-week protocol. There was also no significant difference between the 2 groups in the proportion of subjects who completed the entire course of treatment ($\chi^2 = 0.11$, $P = .74$). Among subjects completing the 12 weeks of treatment, medication compliance was 88.6% (10.9%) and 92.1% (10.0%) in the treatment and placebo groups, respectively ($P = .30$).

Weight Loss

Primary Analysis.—The weight loss curves for placebo and treatment groups are shown in Figure 2 for subjects in the intent-to-treat analysis with LOCF. The estimated mean (SD) [median (interquartile range)] weight loss for the placebo group was 4.1 (3.9) [3.9 (4.7)] kg and for the treatment group was 3.2 (3.3) [2.6 (4.1)] kg. The weight loss within each group was significantly different from baseline ($t_{134} = 11.795$, $P<.001$), although between-group weight loss differences were not statistically significant ($t_{133} = 1.474$, $P = .14$). Body weight change differences remained nonsignificant after controlling for patient starting weight, sex, and age. Assumptions of the applied parametric statistical analysis such as homogeneity of variance and normality of residuals were tested and no meaningful violations were detected. Given the lack of significant findings, questions of statistical power are important. Therefore, using the observed distributions of weight change and the within-group SD thereof, we estimated that the power of the current study to detect differences between the treatment and placebo groups in terms of weight change was 89% to detect a between-group difference in weight loss as small as 2 kg at the 2-tailed α level of .05.

Secondary Analyses.—In no case did any secondary analysis indicate any statistically significant effect for the active compound to produce more weight loss than placebo.

Fat Mass Loss

Primary Analysis.—Results for body fat mass analysis were imputed for 9 baseline and 4 post–weight loss subjects. With the LOCF intent-to-treat analysis, the estimated mean (SD) [median (interquartile range)] percentage of body fat mass loss for the placebo group was 2.16% (2.06%) [2.20% (2.7%)] and the estimated percentage of fat mass loss for the treatment group was 1.44% (2.15%) [1.60% (1.9%)]. This difference was tested using the Welch test because the variances were significantly hetero-
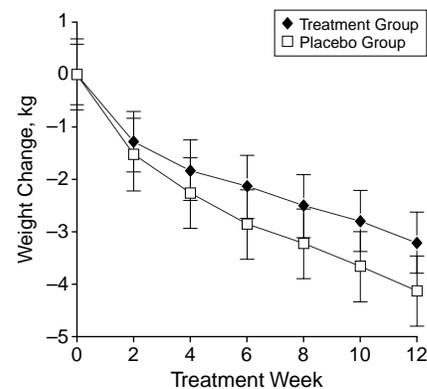
geneous by the Levene test (P for variance heterogeneity = .03). Using the Welch test, the placebo and treatment group mean differences were not statistically significant ($t_{129} = 1.7$, $P = .08$). This finding was consistent with that of the ordinary t test ($t_{132} = 1.78$, $P = .08$). Using analysis of covariance with age, sex, and pretest percentage of fat mass as covariates, the percentage of fat mass differences also was nonsignificant ($F_{1,129} = 1.57$, $P = .21$).

Secondary Analyses.—As for weight loss, all of the secondary analyses were consistent with the primary analysis. That is, in no case did analysis indicate any statistically significant effect for the active compound to produce a different percentage of body fat mass loss than the placebo.

Examination of the change in fat mass relative to change in body weight derived using least squares regression analysis for all subjects combined resulted in the relation, Δfat mass (kg) = $0.77 \times$ Δbody weight (kg) – 0.44, with $r = 0.89$ and $P<.001$. The association was not changed significantly ($P>.91$) by adding treatment group as a second independent variable, even after adjusting for 3 additional potential covariates: initial body weight, sex, and age.

Adverse Events

No patient was removed from the study protocol for a treatment-related adverse event, and the number of reported adverse events was not significantly different between the placebo and treatment groups (eg, headache, 12 vs 9, respectively; upper respiratory tract symptoms, 13 vs 16, respectively; and gastrointestinal tract symptoms, 6 vs 13, respectively).

Table 2.—Summary of Previous *Garcinia cambogia* Studies*

Author(s)	Publication Type	Study Design	Study Agent(s)	Sample	Duration, wk	Major Observations
Badmaev and Majeed[10]	Industrial	Single arm, open label	GCE, 500 mg, chromium picolinate, 100 μg, 3 times per day and healthy eating/exercise	77 obese adults, with 55 completing trial	8	5.5% weight loss in women, 4.9% in men†; combined, $P<.001$ vs baseline
Conte[11]	Peer-reviewed	Randomized, double-blind, placebo controlled	*Garcinia indica* extract 500 mg, nickel chromium, 100 μg, 3 times per day and low-fat substitution diet	54 obese subjects randomized, with 39 completing trial	8	Active, 11.14 lb, vs placebo, 4.2 lb†‡
Ramos et al (unpublished data)	Abstract	Randomized, double-blind, placebo controlled	GCE, 500 mg, 3 times per day, and low-fat 4200-6300 kJ/d diet	40 obese subjects randomized, with 35 completing trial	8	Active, 4.1 (1.8) kg, vs placebo, 1.3 (0.9) kg ($P<.05$)§
Kaats et al (unpublished data)	Abstract	Randomized, double-blind, placebo controlled	GCE, 1500 mg/d, chromium picolinate, 600 μg/d, L-carnitine, 1200 mg/d, and low-fat, high-fiber diet	200 subjects randomized, with 186 completing trial	4	Active, −2.84 lb, vs placebo, −1.4 lb fat mass loss ($P<.01$)†
Thom[12]	Abstract	Randomized, double-blind, placebo controlled	Hydroxycitric acid, 1320 mg/d, in 3 divided doses, and 5040-kJ/d low-fat diet	60 subjects randomized; number completing trial not reported	8	Active, 6.4 kg, vs placebo, 3.8 kg weight loss ($P<.001$); weight loss as fat, 87% in active vs 80% in placebo group†‡
Rothacker and Waitman[13]	Abstract	Randomized, double-blind, placebo controlled	GCE, 800 mg, natural caffeine, 50 mg, and chromium polynicotinate, 40 μg, 3 times per day, and 5040-kJ/d diet	50 obese subjects randomized, with 48 completing trial	6	Active, −4.0% (3.5%) vs placebo, −3.0% (3.1%) body fat mass ($P=.30$)
Girola et al[14]	Peer-reviewed	Randomized, double-blind, placebo controlled	GCE, 55 mg, chrome, 19 mg, and chitosan, 240 mg; randomized to 1 of 3 groups, active medication twice per day, placebo twice per day, or 1 placebo and 1 active medication per day; all groups treated with hypocaloric diet	150 obese subjects; number completing trial not reported	4	Active, twice per day, −12.5% (1.2%); active, once per day, −7.9% (0.9%); twice per day placebo, −4.3% (1.0%); "overweight reduction" ($P<.01$ for all 3 vs baseline)§

*GCE indicates *Garcinia cambogia* extract.
†No SDs reported.
‡No statistical analysis reported
§Numbers in parentheses are SD.

COMMENT

In 1883 von Lippmann isolated hydroxycitric acid, a minor constituent of sugar beets.[27] More than half a century later, in 1941, Martius and Maué[28] discovered that the (+) isomer of a racemic hydroxycitric acid mixture is attacked by the enzyme isocitrate dehydrogenase. The (−) hydroxycitric acid isomer of hydroxycitric acid was first isolated by Lewis and Neelakantan in 1964,[29] and by 1969 Watson and colleagues[5] reported the powerful inhibition by (−) hydroxycitric acid of citrate cleavage enzyme. Evidently, the additional hydroxyl group's steric position, compared with citric acid, enhances its binding affinity and competitively inhibits catalytic action by the enzyme. Citrate, entering the cytoplasm from mitochondria, cannot be cleaved to release acetyl coenzyme A, the substrate for de novo fatty acid synthesis. Despite these century-old, well-grounded observations, there has been little effort to critically test the basic assumption underlying therapeutic use of hydroxycitric acid in overweight humans: that hydroxycitric acid inhibition of lipid synthesis will significantly reduce body fat mass beyond that observed with a placebo capsule.

The present study, carried out during a 12-week evaluation period and using accepted experimental design and in vivo analytic methods, failed to support the hypothesis that hydroxycitric acid as prescribed promotes either additional weight or fat mass loss beyond that observed with placebo. Specifically, body weight and fat mass change during the 12-week study period did not differ significantly between placebo and treatment groups. These results apply to both the primary and secondary statistical analyses. Additionally, there were no observed selective fat-mobilizing effects specifically attributable to the active agent, hydroxycitric acid.

Seven earlier *G cambogia* trials have appeared in peer-reviewed literature,[11,14] as abstracts,[12,13] and in industrial publications as an open-label study[10] and randomized controlled trials.[11-14] We chose to collectively review these studies even though *G cambogia* typically was used in combination with other ingredients for the claimed purpose of enhancing weight loss. Of the 7 studies reviewed, 5 reported significant ($P<.05$) effects of *G cambogia* alone or in combination with other ingredients on body weight or fat mass loss in overweight humans (Table 2). These earlier studies all have limitations when specifically considering *G cambogia* as a weight loss agent, including lack of placebo control or double-blinding in 1 study,[10] coadministration of *G cambogia* in combination with other potentially active ingredients in 5 studies,[10,11,13,14] use of an inaccurate body composition method (near-infrared interactance)[12] in 1 study, and failure as of yet to publish study results in peer-reviewed literature in all but 2[13,14] of the 7 studies. However, our present investigation, carried out using accepted clinical trial design procedures and applying accurate body composition methods, failed to support a specific weight loss effect of *G cambogia* administered as recommended. The present 12-week study period also exceeded in duration all previous study treatment periods, which ranged from 4 to 8 weeks.

In our present investigation we failed to detect a weight loss or fat-mobilizing effect of active herb. The question therefore arises whether there exist conditions differing from those used in the present study that might support hydroxycitric acid efficacy. The 5040-kJ/d low-fat diet recommended in our current study was intended to mimic diets commonly prescribed as a component of weight control programs. The possibility exists that the lipid synthesis–inhibiting properties of hydroxycitric acid may be more evident in subjects relapsing following a failed diet attempt, particularly if high-carbohydrate foods are ingested.[30]

Another concern is related to the timing and dosage considerations of hy-

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droxycitric acid. Sullivan and colleagues[31] showed that the effects of hydroxycitric acid in animals depend on time of administration in relation to a meal, with hydroxycitric acid maximally effective when administered 30 to 60 minutes prior to feeding. The approach used in our study and the others we reviewed suggested hydroxycitric acid ingestion about 30 minutes prior to meal intake, the lower end of the maximally effective range. A related concern is that hydroxycitric acid provided in divided doses also was found to be more effective than the same amount given as a single dose.[8] Although divided doses typically are used in weight loss protocols, human doses ranging between 750 and 1500 mg/d of hydroxycitric acid are at the extreme low end of the in vivo dose-response range established by Sullivan and colleagues.[32] Thus, in light of the many requirements for its effective use, it seems unlikely that the maximal effects of hydroxycitric acid will be realized in human weight loss studies unless treatment conditions are well defined

and patient diet and medication compliance are tightly monitored.

Our study explored product safety only in the form of clinical evaluations and reported adverse events. No significant differences were observed between placebo and treatment groups in number of reported adverse events and no subjects were removed from the study for a treatment-related adverse event. Additional studies, potentially with larger subject groups, are needed to gather specific information on the long-term safety of *G cambogia*.

An important concern in all pharmacological trials, particularly those in which herbal products are evaluated, is the amount and bioavailability of the active agent. As standard procedure, we confirmed the presence and quantity of hydroxycitric acid in the supplied capsules using an independent testing laboratory. However, we did not measure hydroxycitric acid blood levels or evaluate tissue or cytosolic citrate-cleavage enzyme activity. Although the format of our experiment closely resembles cur-

rent use of *G cambogia* as a weight loss product, our conclusions should not be interpreted as a failure to support the validity of the biochemical effects of hydroxycitric acid identified by earlier investigators.

In conclusion, our study evaluated the hypothesis that the active ingredient of *G cambogia*, hydroxycitric acid, has beneficial weight and fat mass loss effects. Our findings, obtained in a prospective, randomized, double-blind study, failed to detect either weight loss or fat-mobilizing effects of hydroxycitric acid beyond those of placebo. These observations, the first, to our knowledge, to appear in a peer-reviewed article using currently accepted experimental and statistical methods, do not support a role as currently prescribed for the widely used herb *G cambogia* as a facilitator of weight loss.

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