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Effects of (−)-hydroxycitric acid on appetitive variables

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Abstract

(−)-Hydroxycitric acid (HCA) reportedly promotes weight loss, in part, through suppression of hunger. However, this mechanism has never been evaluated in humans in a controlled study. Eighty-nine mildly overweight females were prescribed 5020-kJ diets for 12 weeks as part of a double-blind, placebo-controlled parallel group study. Forty-two participants ingested 400-mg caplets of *Garcinia cambogia* 30–60 min prior to meals for a total dose of 2.4 g/day (1.2 g/day HCA). Forty-seven participants ingested matched placebos. Weight and body composition were assessed at baseline and every other week for 12 weeks. Food intake and appetitive variables were assessed at baseline and monthly for 12 weeks. Both groups lost body weight with the active group achieving a significantly greater reduction (3.7 ± 3.1 kg versus 2.4 ± 2.9 kg). No effects of the HCA were observed on appetitive variables. The active treatment group did not exhibit better dietary compliance or significant correlations between appetitive variables and energy intake or weight change. This study does not support a satiety effect of HCA.

Keywords: *Garcinia cambogia*; Hydroxycitric acid; Hunger; Weight loss; Human; Appetite

1. Introduction

Dietary approaches for the management of obesity have been largely unsuccessful due, in part, to feelings of hunger that undermine adherence to weight loss regimens. Pharmacologic agents designed to suppress hunger have promoted weight loss, but are often accompanied by unacceptable side effects. Amphetamine-based anorexiants are effective in some patients, but leave them feeling anxious and are prone to abuse and chemical dependency [33]. This limits their long-term use and cessation typically results in prompt regain of body weight. Beta-phenethylamine derivatives have lower abuse potential but may still cause insomnia, anxiety and irritability [33]. While useful in many patients, their limited efficacy prompted research into a new class of agents, ones acting on serotonergic neurotransmission. Dexfenfluramine hydrocholoride and fenfluramine hydrochloride were widely effective, but were implicated in the development of cardiac valvulopathy [15] and withdrawn from the market. The most recent introduction in this class of drugs, Sibutramine, a serotonin-and norepinephrine-reuptake inhibitor, appears promising, but may increase blood pressure and heart rate in some patients [16]. It also has the potential to promote dependency if abused [16]. Attempts to manipulate satiety hormones such as cholecystokinin or bombesin to achieve sustained weight loss have proven elusive [17].

The limited success and potential complications of these pharmacologic weight loss aids has led to a large and growing market for alternative therapies such as herbal products. *Garcinia cambogia*, grown primarily in Southeast Asia, is one popular representative. The dried and cured pericarp of the fruit of this species contains up to 30% by weight of (−)-hydroxycitric acid (HCA) [19]. These rinds are used in regional cooking practices and are reported to make meals more filling [4]. This claim is bolstered by cursory observations from clinical studies [2]. A satiety effect has been demonstrated experimentally in rats and associated with weight reduction [26,36,37]. Because HCA does not appear to enter the brain, it does not elicit CNS side effects that may limit its acceptability.

HCA may promote weight reduction through suppressed de novo fatty acid synthesis, increased lipid oxidation and reduced food intake [22]. Enhanced satiety may account for the reported suppression of energy consumption. One potential mechanism accounting for the

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satiety effect of HCA may involve inhibition of ATP citrate lyase. This would limit the availability of acetyl coenzyme A (acetyle CoA) for lipid synthesis during carbohydrate feeding. As a result, carbon is diverted to glycogen synthesis. Based primarily on studies with mice [7,8] and rats [24], it has been argued that glycogen levels serve as a primary signal for energy regulation. However, this has been questioned by findings from human clinical trials [31,34]. Further, the efficiency of carbohydrate conversion to fat under conditions of energy excess in humans is extremely low [13] so inhibition of this pathway would be expected to hold limited consequence.

A second possible mechanism for an anorectic effect of HCA holds that by reducing acetyl CoA, malonyl CoA levels are depressed thereby reducing negative feedback on carnitine acyltransferase [21]. This leads to increased lipid transport into the mitochondria and inefficient oxidation with resultant ketone body formation. Ketones are purported appetite suppressants, however, several groups have failed to observe an association between ketosis and reported hunger level [3,32].

Despite an hypothesized prominent role of HCA-induced satiety on reduced energy intake and weight loss, there has been little experimental evaluation of this action in humans. Given the mechanistic issues raised above, recent evidence that HCA may not promote weight loss [14] and widespread use of products containing HCA for weight management, the question of whether HCA is an appetite suppressant warrants further consideration. The present study was designed to assess the effect of *G. cambogia* on appetitive indices and their relationship with weight loss during moderate energy restriction.

2. Methods

2.1. General protocol

Participants were recruited by public advertisement into a randomized, double-blind, placebo-controlled, parallel-group design study. During an initial baseline visit, all participants completed health, demographic and dietary restraint questionnaires, had their body weight and composition determined, completed chemosensory function tests and received dietary guidance. They were then randomly assigned to receive either caplets of *G. cambogia* or placebo. A log of hunger ratings and activities was kept over the next 24 h. During that week, participants were called twice and asked to keep 24-h diet records. One week after the initial meeting, they began their 12-week diet. Exercise was encouraged, but no formal regimen was prescribed. Diet records and hunger and activity logs were kept and chemosensory function was assessed during weeks 4, 8 and 12. At the end of weeks 2, 4, 6, 8, 10 and 12, participants reported to the laboratory for repeat assessments of body weight and composition. The protocol was approved by the Human Subjects Review Committee of Purdue University.

2.2. Subjects

Participant eligibility criteria included: 18–65 years old; 10–50 lb over ideal body weight [23]; interested in losing 10–20 lb; not adhering to any prescribed diet or taking medications (except birth control); and self-reported normal taste and smell function. A total of 167 individuals were recruited. An error in coding of pill bottles provided to the researchers (detected after the study, but prior to data analyses) resulted in 28 participants receiving a mixture of active and placebo pills. Thus, these participants were excluded from analyses. Based upon pill counts (ingestion of at least 80% of the administered caplets) and attendance at requisite evaluation sessions, a total of 106 individuals were deemed compliant with study procedures. Among the non-compliant group, 20 had been assigned to active treatment and 13 to placebo. Only 17 of the eligible sub-sample were male. Because the small number of males precluded meaningful gender-specific analyses and there are reports of sex differences in appetitive ratings [24,28,43], including to HCA treatment [2], as well as well known differences in energy intake, analyses were focused on the 89 compliant females. Eighty-seven participants were Caucasian, with one African American and one Asian. Table 1 contains other baseline characteristics of the total sample as well as the active treatment and placebo treatment groups. Only disinhibition scores differed significantly between groups ($t = 2.07$, $p = 0.042$).

Table 1
Participant characteristics

	Total sample ($N = 89$)	Active treatment ($N = 42$)	Placebo treatment ($N = 47$)
Age (years)	42.7 ± 10.0	40.97 ± 10.4	44.0 ± 9.5
Body mass index (kg/m^2)	28.6 ± 0.5	28.3 ± 0.6	28.8 ± 0.7
Body weight (kg)	75.6 + 11.5	75.5 + 10.2	75.8 + 12.6
% Body fat	33.6 ± 12.7	32.4 ± 9.0	34.8 ± 15.3
Weight loss goal (kg)	12.9 ± 6.5	12.1 ± 5.3	13.7 ± 7.4
Cognitive restraint (Three-Factor Eating Questionnaire (TFEQ))	9.6 ± 4.2	9.8 ± 3.8	9.6 ± 4.5
Disinhibition (TFEQ)	8.7 ± 3.4	7.9 ± 3.2	9.3 ± 3.4
Hunger (TFEQ)	6.3 ± 3.1	6.3 ± 3.0	6.2 ± 3.3

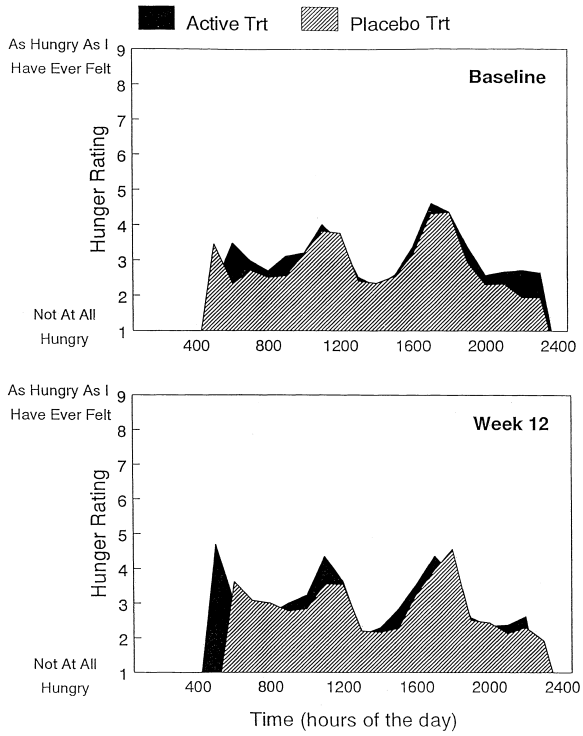

Fig. 1. Self-reported hourly hunger ratings obtained over a 24-h period on a nine-point category scale during the pre-treatment week and week 12 of treatment by participants receiving active treatment or placebo.

2.3. Treatment

Participants were counseled to adhere to a 1200-kcal exchange diet [1] that contained about 30% of energy from fat. They were provided reference materials, recipes and trained to estimate portion sizes with true-size portion charts. Active treatment participants were required to ingest two 400-mg caplets of *G. cambogia* or matched placebo three times per day (30–60 min before each meal). The source of HCA used in the study was *G. cambogia* extract (Citrin® standardized for a minimum of 50% HCA). Its purity was determined by HPLC. Thus, the total dose of HCA in the active treatment group was 1.2 g/day. Placebo treatment participants took identical caplets at the same schedule.

2.4. Appetitive questionnaires

Hunger, desire to eat, prospective consumption (how much food do you think you could eat right now?) and fullness (the primary appetitive questions) were evaluated by having participants indicate the intensity of the sensation they ascribed to each on a nine-point category scale each waking hour for 1 day at baseline and during weeks 4, 8 and 12. End anchor descriptors are listed in Figs. 1 and 2. In addition, participants indicated how intensely they experienced feelings of stomach growling, headache, thirst, irritability, itchiness and distractability (the ancillary appetitive questions) on scales ranging from "not at all" to "extremely." During another baseline day and weeks 4, 8 and 12, participants also coded hunger by outlining the place(s) on a gender-appropriate human figure where they felt the sensations they associate with hunger occurred [9] These areas were cut out of the form and weighed. They were coded into three regions — head and neck, trunk, limbs.

2.5. Restraint

Dietary restraint was assessed by the TFEQ [35].

2.6. Body weight and composition

Body weight was measured on a clinical scale with subjects wearing only a hospital gown. They voided just prior to weighing. Measurements were obtained at approximately the same time of day for each individual. Fat mass, fat-free mass and body water were determined by bioelectrical impedance analysis (Tanita Body Fat Analyzer, TBF-105, Tanita, Skokie, IL).

2.7. Dietary assessment

Energy and nutrient intake were determined with version 7.2 of The Food Processor nutrient database (ESHA Research, Salem, OR).

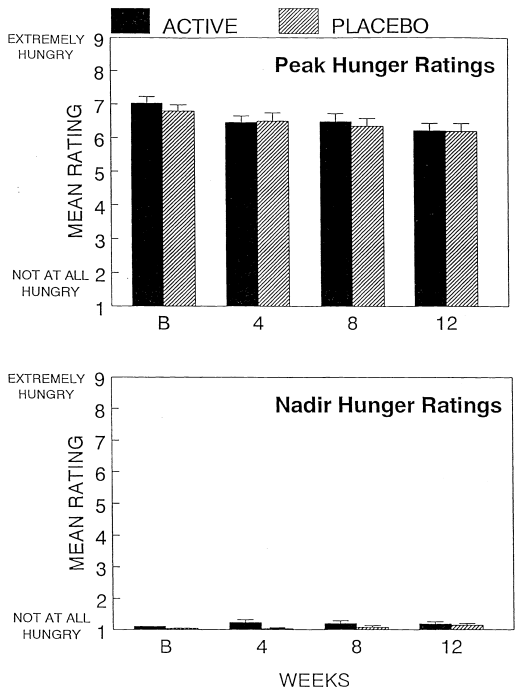

Fig. 2. Mean (±SE) peak and nadir self-reported hunger ratings obtained over a 24-h period prior to treatment (B) or at weeks 4, 8 and 12 of treatment with active compound or placebo.

2.8. Energy expenditure

Energy expended in physical activity was determined by questionnaire [30] completed at baseline and weeks 4, 8 and 12.

2.9. Sensory function

Participants rated an array of commercially available foods for sensation intensity using nine-point category scales with end anchors of "no (sweetness, saltiness, fat) at all" and "extremely (sweet, salty, high fat)." Pleasantness was also rated on a nine-point category scale with end anchors of "extremely pleasant" and "extremely unpleasant." Single bite-sized samples of foods were presented in random order and consumed. A water rinse was interspersed between samplings. Ratings were obtained at baseline and weeks 4, 8 and 12. Seventeen foods were selected to be representative of eight overlapping general categories.

Low sweet–low fat	Peaches Lite (Del Monte Foods, San Francisco, CA), Golden Loaf, fat-free and cholestrol-free (Entemanns Foods, Totowa, NJ)
High sweet–low fat	Glazed Donuts Light (Entemanns Foods), Peaches in Heavy Syrup (Del Monte Foods), Fat-Free Vanilla Ice Cream (Prarie Farms Dairy, Carlinville, IL)
Low sweet–high fat	All Butter Loaf (Entemanns Foods)
High sweet–high fat	Glazed Buttermilk Donuts (Entemanns Foods), Vanilla Ice Cream (Prarie Farms Dairy), Honey-Roasted Peanuts (Nabisco Foods, Winston-Salem, NC)
Low salt–low fat	White Corn, air-popped (American Popcorn, Sioux City, IA), Unsalted Original Sourdough Recipe Hard Pretzels (Wege Pretzel, Hanover, PA)
High salt–low fat	Original Sourdough Pretzels (Wege Pretzel), Low-Fat Original Potato Crisps (Frito-Lay, Plano, TX)
Low salt–high fat	White Corn, air-popped (American Popcorn), coated with salt-free butter (Land O' Lakes, Arden Hills, MN), Unsalted Cocktail Peanuts (Nabisco Foods)
High salt–high fat	Cocktail Peanuts (Nabisco Foods), Potato Chips (Frito-Lay)

2.10. Statistical analysis

Body weight, energy and macronutrient intake, appetitive ratings and sensory function were explored by repeated measures analysis of variance with treatment as a between group factor. Where appropriate, paired *t*-tests were used for post hoc comparisons. For the appetitive variables, the primary metric used was the mean self-reported rating during the time each individual was awake on a recording day. Associations between the appetitive variables and both dietary intake indices and weight loss outcome were assessed by Pearson correlation coefficients. The criterion for statistical significance was set at $p < 0.05$, but where multiple comparisons were conducted, the Bonferroni correction was applied.

3. Results

A statistically significant loss of weight was observed over the 12-week study period in both the active ($t = 7.80$, $p < 0.001$) and placebo ($t = 5.65$, $p < 0.001$) treatment groups. The mean loss with active treatment was 3.7 ± 3.1 kg whereas the value was 2.4 ± 2.9 kg for the placebo group. The difference in weight loss between groups was also statistically significant ($t = 2.26$, $p = 0.026$). The decrease in fat mass was not significantly different between groups (active = -4.1% and placebo = -3.0%), but the reduction in waist circumference was significant (active = -3.96 cm, placebo = -2.22 cm ($t = 2.72$, $p = 0.008$)). Relative to baseline, both groups reported significant reductions in energy consumption during the diet period (-1756 ± 409 kJ/day — active, -1574 ± 322 kJ/day — placebo). Mean daily intake tended to be lower during active treatment compared to placebo (5534 ± 315 versus 6191 ± 239 kJ/day), but the difference was not significant ($t = 1.68$, $p < 0.1$). There was no significant group difference in energy expenditure at any time point or a change over time.

Fig. 1 depicts the hunger patterns of participants at baseline and the end of the 12-week study. Because participants awoke and retired at different times of day, data are presented only when ≥ 10 participants were awake. Between 800 and 2200 h, ≥ 30 individuals were awake in each group. Ratings were coded as missing when participants were asleep. While hunger did change over the 24-h recording periods (e.g, baseline — $F(14,728) = 8.44$, $p < 0.001$; week 12 — $F(14,560) = 8.93$, $p < 0.001$), no significant group differences were observed at any time point during baseline or weeks 4, 8 or 12. Mean ratings were also comparable across the study period. Peak and nadir values were similar between the groups at baseline and at the end of weeks 4, 8 and 12 and were stable over the study period (Fig. 2). Group variance in reported hunger was significantly greater in the active treatment group at baseline (F test for variance, $p < 0.05$), but the group variances during treatment were not significantly different.

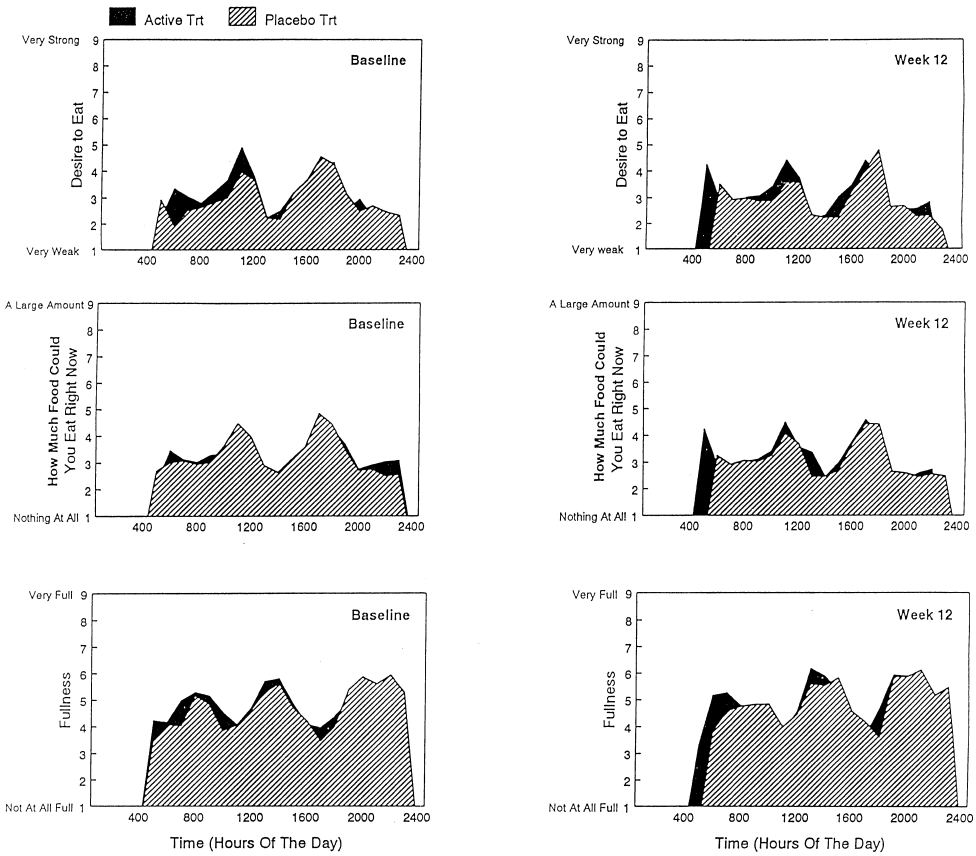

Fig. 3. Self-reported hourly "desire to eat," "prospective consumption" and "fullness" ratings obtained over a 24-h period on a nine-point category scale during the pre-treatment week and week 12 of treatment by participants receiving active treatment or placebo.

The patterns of responses for desire to eat, prospective consumption and fullness at baseline and week 12 are presented in Fig. 3. Active treatment participants reported a higher desire to eat than the placebo treated participants only at 600 h during baseline ($t=3.07$, $p=0.004$). This isolate finding is likely artifactual. Fullness and prospective consumption ratings were similar at all time points from baseline to the end of the study.

Table 2 contains self-reported 24-h mean appetite-related sensations by active and placebo treated participants at baseline and weeks 4, 8 and 12. Mean thirst ratings were higher during baseline relative to all other assessments (all $p<0.05$) in the full sample. However, the treatment effect and time by treatment interaction were not significant. No other significant treatment or time effects were observed. Ratings of itchiness, which were not expected to vary in relation to the treatment, also did not differ between groups or over time.

With a correction for multiple testing, there were no significant group differences in the rated sweetness, saltiness, fat level or pleasantness of the test foods at baseline or any time during treatment.

Baseline mean appetitive sensations did not correlate significantly with weight change in the full sample (Pearson correlation coefficients ranged from -0.19 (hunger) to 0.05 (fullness), placebo sub-group ($r=-0.24$ (hunger) to 0.12

Table 2
24-h mean (SD) appetite-related sensations (and a malingering check "itchiness" at baseline and weeks 4, 8 and 12 treatment for participants receiving active treatment and placebo. Ratings of 1.0 = not at all, 9.0 = extremely

	Baseline		Week 4		Week 8		Week 12	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
Thirst	2.9±1.4	3.3±1.7	2.9±1.6	2.8±1.6	2.5±1.2	2.8±1.4	2.7±1.4	2.7±1.5
Stomach growl	1.8±0.6	1.7±0.6	1.6±0.5	1.6±0.7	1.6±0.6	1.6±0.6	1.7±0.7	1.5±0.5
Headache	1.5±0.7	1.4±0.4	1.5±1.2	1.4±0.6	1.3±0.5	1.3±0.5	1.5±0.8	1.2±0.4
Distracted	1.4±0.7	1.5±0.9	1.6±0.6	1.6±0.8	1.3±0.7	1.6±1.2	1.3±0.8	1.5±0.9
Irritable	1.5±0.8	1.3±0.6	1.4±0.6	1.3±0.5	1.3±0.6	1.4±0.8	1.4±0.6	1.4±0.8
Itchiness	1.1±0.2	1.1±0.2	1.0±0.0	1.1±0.3	1.1±0.2	1.1±0.2	1.2±0.5	1.2±0.6

(fullness)) or active treatment sub-group ($r = -0.08$ (hunger) to 0.26 (fullness)). Among the placebo-treated participants, the only appetitive variable significantly correlated with weight change was mean hunger ratings at week 8 ($r = -0.40$, $p = 0.01$). No significant associations were observed in the active treatment group at any time point. Similarly, correlations between appetitive variables and energy intake or change of energy intake were of a low order and not-statistically significant. Among active treatment participants, correlation coefficients between hunger ratings at baseline and treatment weeks 4, 8 and 12 ranged from -0.21 to 0.02 for energy intake and from -0.16 to 0.20 for change of energy intake from baseline. Correlations between the appetitive variables of desire to eat, prospective consumption and fullness and the intake variables of energy consumption and change of energy consumption ranged from -0.30 to 0.27.

4. Discussion

Consistent with the prescribed and reported reduction of energy intake, participants in both the active and placebo treated groups lost weight over the study period. The active treatment group achieved a significantly, albeit modest in absolute terms, greater reduction. This finding is consistent with several early reports [5,38], but not with a recent, larger and more vigorously controlled trial [13]. However, such comparisons must be made with caution as there were differences in the formulations and doses administered and study populations. Earlier reports were typically based on combination products (e.g., HCA plus chromium) (e.g., Ref. [2,5,10]) so efficacy cannot be ascribed to the HCA alone. Interestingly, more consistent weight loss is reported with lower doses of HCA (i.e., approximately 750 mg/day [2,5,10]) compared to higher doses (i.e., 1300–1500 mg/day [14,29,39]). Further, several had small sample sizes [5,39] and/or lacked a placebo control [2]. The work by Heymsfield et al. [14], which yielded no effect, involved males and females whereas the present report is limited to females. In fact, the males in our study exhibited more variable weight responses and if included in the sample, the significant difference from placebo treatment was eliminated. Heymsfield et al. [14] reported controlling for gender did not influence their findings, but our data suggest a gender-specific weight-loss response remains a possibility. Additionally, studies of rats suggest obese animals are more resistant to the weight reducing effects of HCA than the lean [11]. The study population used by Heymsfield et al. [14] included a higher proportion of markedly obese individuals than the present sample.

The primary focus of our work concerned the effects of HCA on appetitive variables and whether these could account for any noted effects on weight loss. The association between appetitive sensations, food intake and body weight is weak in non-dieting and dieting, free-living individuals [6,20,26,40,41] but pharmacologic enhancement of satiety has proven effective at reducing energy intake and weight [12,25]. The present data on appetitive indices are unequivocal. No significant treatment effects were observed on mean, peak or nadir hunger ratings, mean ratings of desire to eat, prospective consumption, fullness or sensations of thirst, stomach growling, headache, distraction, irritability or, as a check on malingering, itchiness. Prior support for an appetitive effect was based on anecdote [4] and data interpreted without a control treatment or pure HCA formulation [2]. The appetitive indices also were not significantly associated with energy intake or body weight change within the active treatment participants. An association between satiety effects and weight reduction has been reported in rats [27,37,38]. However, the effect is transient [11]. The association was examined at weeks 4, 8 and 12 of this study and was not apparent at any time point. It is possible that it lasted less than 4 weeks. A diminution of appetite suppression over this time frame has been noted [2] yet, interestingly, weight loss reportedly continued in that study. The weak and transient nature of appetitive effects of HCA raise questions about its clinical significance. While negative findings are always open to methodological questions, the consistency of our data across appetitive indices, larger sample size and use of more rigorous methodology lends credence to our findings. Unlike most other published work, our study also entailed ingestion of the active pills 30–60 min prior to meals when, based on animal studies, the HCA reaches peak efficacy [36]. The administered dose was modest and blood samples were not collected to confirm effective plasma levels were achieved, but the weight loss results suggest the dose was adequate to elicit physiological effects.

Increased blood ketones and hepatic or muscle glycogen levels have been posited as potential mechanisms for the satiety effect of HCA [21,22]. These indices were not measured in the present study but two recently published trials [14,18], involving participants on diets with macronutrient compositions similar that used here, have failed to note shifts associated with HCA use.

Alteration of the rewarding properties of foods can lead to reduced intake independent of hunger status [42]. However, the lack of effect of HCA on either taste intensity or hedonic ratings for foods suggests this also is unlikely to account for the present findings.

To the extent that hunger sensations are sufficiently unpleasant that they compromise dietary compliance, it was hypothesized HCA would lead to higher rates of dietary adherence relative to placebo-treated controls. However, study attrition rates were comparable in the two groups (20 from active and 13 from placebo), as noted by others [14]. These data suggest the addition of HCA does not promote improved compliance with a reduced energy diet. However, given the lack of effect on hunger, they do not address the more general question of whether amelioration of hunger serves this function.

There are several qualifications that warrant comment in this study. First, the study of appetitive properties of HCA under conditions of energy restriction could be viewed as problematic if the diet promoted extreme sensations. However, this did not occur with the mild restriction imposed as evidenced by ratings falling in the middle range of the response scales. Second, given that an energy-restricted diet would prevent the required enzyme alterations (acetyl CoA–malonyl CoA) that lead to altered substrate metabolism and satiety, the concurrent dietary restriction could have hampered induction of HCA's satiety effects. However, the prescribed diet was only mildly energy restricted and still contained at least 30% of energy from fat. Thus, it likely reflected conditions under which HCA would be used by consumers. Third, it may be that HCA is more effective at moderating weight gain [11] than promoting weight loss. This was not tested, but if true, the compound may be more useful for weight maintenance after an initial loss.

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