EXHIBIT A

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy
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ORIGINAL RESEARCH

Randomized, double-blind, placebo-controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects

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Background: Adult weight gain and obesity have become worldwide problems. Issues of cost and potential side effects of prescription weight loss drugs have led overweight and obese adults to try nutraceuticals that may aid weight loss. One promising nutraceutical is green coffee extract, which contains high concentrations of chlorogenic acids that are known to have health benefits and to influence glucose and fat metabolism. A 22-week crossover study was conducted to examine the efficacy and safety of a commercial green coffee extract product GCA™ at reducing weight and body mass in 16 overweight adults.

Methods: Subjects received high-dose GCA (1050 mg), low-dose GCA (700 mg), or placebo in separate six-week treatment periods followed by two-week washout periods to reduce any influence of preceding treatment. Treatments were counterbalanced between subjects. Primary measurements were body weight, body mass index, and percent body fat. Heart rate and blood pressure were also measured.

Results: Significant reductions were observed in body weight (−8.04 ± 2.31 kg), body mass index (−2.92 ± 0.85 kg/m^2), and percent body fat (−4.44% ± 2.00%), as well as a small decrease in heart rate (−2.56 ± 2.85 beats per minute), but with no significant changes to diet over the course of the study. Importantly, the decreases occurred when subjects were taking GCA. Body mass index for six subjects shifted from preobesity to the normal weight range (<25.00 kg/m^2).

Conclusion: The results are consistent with human and animal studies and a meta-analysis of the efficacy of green coffee extract in weight loss. The results suggest that GCA may be an effective nutraceutical in reducing weight in preobese adults, and may be an inexpensive means of preventing obesity in overweight adults.

Keywords: green coffee bean extract, chlorogenic acid, body mass index, weight loss, body fat mass, blood pressure, heart rate

Introduction

The World Health Organization predicts there will be 2.3 billion overweight adults in the world by 2015, and more than 700 million of them will be obese. Worldwide obesity has more than doubled since 1980. In 2008, 1.5 billion adults, 20 years of age and older, were overweight. Of these, over 200 million men and nearly 300 million women were obese. Over 65% of the world population lives in countries where overweight and obesity kills more people than underweight.[1] With the high cost of prescription weight loss drugs and the fear of side effects, the general public is turning to nutraceuticals. The estimated global market for 2014 is over 350 billion US dollars, as published by Market Research News.[2]

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At the present time, there is only one nonprescription nutraceutical product that is currently under investigation (Pharmachem Laboratory, Phase II) and is approved by the US Food and Drug Administration, with a qualified health claim for assistance in weight control and a structure-function claim for its mechanism, which is that it blocks starch absorption by means of an α-amylase inhibitor.[3,4] Coffee is of interest as a possible nutraceutical for weight loss because caffeine is a well known stimulant, and an epidemiology study found that coffee consumption resulted in less weight gain in obese men over an 18-month period.[5] A polysaccharide ingredient in coffee caused weight reduction when added to the diet of obese men but was not effective for women.[6] Freeze-dried coffee was found to cause weight loss when given to rats. It also increased antioxidant enzymes.[7] Caffeine, the major stimulant in coffee, has been linked to weight loss and to reduction in the risk of metabolic syndrome.[8] Existing but limited evidence suggests that substituting coffee for energy-containing soft drinks may facilitate weight management.[9] Several epidemiological investigations have found that coffee consumption reduces the risk of type 2 diabetes, and one of the mechanisms proposed for this benefit is that coffee consumption is inversely associated with weight gain.[10] The purpose of this study was to investigate the efficacy of a high chlorogenic acid green coffee bean extract in reducing weight, body mass, and body fat percentage, in preobese, euthyroid (normal thyroid functioning), otherwise healthy human subjects.

Materials and methods

Subjects

The study included 16 subjects (eight males and eight females) aged 22–46 (mean 33.19 ± 6.75) years. Average body mass index (BMI) at the start of the study was 28.22 ± 0.91 kg/m^2. The mean values for additional measures taken at baseline are listed in Table 1. Subjects exhibited overweight (preobesity) levels, as indexed by BMI 25–30, with the average duration of prevalent BMI being 10.9 ± 3.9 months prior to the onset of the study. Duration of prevalent BMI was determined by examining health records of each subject prior to the beginning of the study. All subjects were euthyroid, nondiabetic (mean blood glucose 107 ± 9 mg/dL), and nonhypertensive (mean systolic/diastolic blood pressure 125.38/81.88 ± 5.10/2.68 mmHg), and were not on or been receiving steroids in the recent past. No subject was on or had been recently on medications known to influence weight for the past 6 months. All subjects had similar diet and exercise profiles and diet was recorded before and at the end of the study (see Table 3 for average diet information). All subjects gave their written informed consent before beginning the study. Informed consent was of a standard format, as per Indian regulatory requirements governing research human subject research, which are consistent with the ethical principles put forth in the Declaration of Helsinki.

Materials

The green coffee extract utilized for this study was provided by Applied Food Sciences Inc (Austin, TX) under the trade name GCA®. GCA contains a standard green coffee extract of total chlorogenic acids assayed at 45.9%, with other hydroxycinnamic acids that are known to have antioxidant health benefits. The total chlorogenic acid and other hydroxycinnamic acid content was 56.66%. Caffeine content was 2%–4% and assayed at 2.60% ± 0.18% for two lots. The relevant polyphenols and caffeine assay was done by ChromaDex Analytical (Irvine, CA) using high-performance liquid chromatography and appropriate standards. This study utilized two dosage levels of GCA, as well as a placebo. The high-dose condition was 350 mg of GCA taken orally three times daily. The low-dose condition was 350 mg of GCA taken orally twice daily. The placebo condition consisted of a 350 mg inert capsule of an inactive substance taken orally three times daily. The two dosages of GCA used here were based on previous

Table 1 Characteristics of 16 preobese subjects at baseline and end of study

Characteristic	Baseline (week 0) M ± SD	End of study (week 22) M ± SD	Difference (week 22 – week 0) M ± SD	Change
Weight (kg)	76.69 ± 7.91	68.65 ± 7.78	–8.04 ± 2.31**	–10.5%
BMI (kg/m^2)	28.22 ± 0.91	25.25 ± 1.19	–2.92 ± 0.85**	–10.3%
Percent body fat	28.13 ± 4.95	23.69 ± 4.95	–4.44 ± 2.00**	–15.8%
HR (bpm)	77.44 ± 4.15	74.88 ± 3.42	–2.56 ± 2.85*	–3.3%
SBP (mmHg)	125.38 ± 5.10	130.25 ± 9.60	4.88 ± 11.24	3.9%
DBP (mmHg)	81.88 ± 2.68	83.38 ± 3.70	1.50 ± 4.41	1.8%

Notes: *$P < 0.005$; **$P < 0.0001$.
Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; M, median; SD, standard deviation.

experience using chlorogenic acids in a human study of the decrease in postprandial glucose.

Study design

This was a randomized, double-blind, 22-week study that implemented a crossover design to compare a low-dose green coffee extract, a high-dose green coffee extract, and a placebo. Subjects were randomly assigned to a high-dose/low-dose/placebo sequence (n = 6), low-dose/placebo/high-dose sequence (n = 4), or placebo/high-dose/low-dose sequence (n = 6). Subjects stayed on a treatment for a period of 6 weeks, followed by a 2-week washout period, before the next treatment period began.

Subjects were examined at weeks 0, 6, 8, 14, 16, and 22 of the study. Subjects were examined individually at Trinity Hospital, Bangalore, India. During each visit, the following measurements were taken: body weight to nearest 0.01 kg, height to nearest 0.01 cm, and a body fat percentage analysis using a SFB7 Bioimpedance device. BMI was determined using the formula of BMI = weight in kg divided by the square of the height in meters. All subjects were counseled for diet and exercise compliance at every visit, with the initial interview to establish diet details at the start of the study done by the site nutritionist. Data gathered included daily calorie intake, nutrient composition, micronutrient intake, and incidence of binge eating (see Table 3 for average diet intake information). The same procedure was repeated at the beginning of each cycle to reflect the diet during the previous cycle and subjects underwent pre- and post-assessment systolic and diastolic blood pressure and heart rate measurements, at every visit. Blood pressure was measured in the right forearm of the subject in a sitting position after a 10-minute rest using a standard mercury sphygmomanometer.

Statistical analysis

The primary measures in this study were weight, BMI, and body fat percentage; however, heart rate and blood pressure taken at each visit were also analyzed. Statistical analyses were carried out with a repeated-measures analysis of variance and post hoc *t*-tests. Factors for the analysis of variance were sequence (high-dose/low-dose/placebo versus low-dose/placebo/high-dose versus placebo/high-dose/low-dose), treatment arm (first versus second versus third treatment), and time (two evaluations per treatment arm). For the time factor, the first evaluation within each treatment arm (weeks 0, 8, 16) was considered a pretreatment evaluation, and the second evaluation within each treatment arm (weeks 6, 14, 22) was a post-treatment evaluation. A statistically significant time × arm interaction indicates drug effects, ie, individually for the high-dose, low-dose, or placebo conditions. A significant sequence × arm × time interaction would indicate significant differences between the drug effects. Finding these interactions significant in the omnibus analysis of variance would validate the comparisons made between the beginning and end data.

Results

The statistical analyses report the test statistic *P* value. From the mean data reported in Table 1 there were statistically significant reductions in weight, BMI, percent body fat, and heart rate after consuming GCA for two-thirds of the 22-week crossover study, but there was no overall significant change in systolic or diastolic blood pressure. The mean values on all measures at the beginning and end of each treatment arm (high-dose, low-dose, placebo) assessed for all 16 subjects, are displayed in Table 2. The data show a reduction in weight, BMI, and percent body fat in the high-dose and low-dose arms, but not the placebo arm, and a reduction in heart rate in the high-dose arm, but not the low-dose and placebo arms. Figure 1 shows the mean weight change across the 22-week study for each of the three groups, and Figure 2 shows the mean change in BMI. A three-way repeated-measures analysis of variance (factor 1: sequence [high-dose/low-dose/placebo versus low-dose/placebo/high-dose versus placebo/high-dose/low-dose]; arm [first versus second versus third treatment]; and time [two evaluations]) on the data from all 16 subjects who were randomized into the crossover design was conducted on each of the primary outcome measures (weight, BMI, and percent body fat), as well as diastolic blood pressure, systolic blood pressure, and heart rate.

Primary outcome measures

There was a significant treatment arm effect for weight ($P < 0.001$), BMI ($P < 0.001$), and percent body fat ($P < 0.001$), showing an improvement in each measure over the course of the study. There was a significant time effect for weight ($P < 0.001$), BMI ($P < 0.001$), and percent body fat ($P < 0.001$), showing an improvement between the beginning and end for each arm. There was no significant difference between the three sequences ($P > 0.373$).

The sequence × arm interaction was significant for weight ($P < 0.004$), BMI ($P < 0.004$), and percent body fat ($P < 0.002$), indicating an overall difference in the arms across the three sequences, ie, a differential influence of each arm on each sequence. The arm × time interaction was

Table 2 Characteristics at start and end of each treatment arm for 16 preobese subjects

Characteristic	HD arm		P	LD arm		P	PL arm		P
	Start M ± SD (95% CI)	End M ± SD (95% CI)		Start M ± SD (95% CI)	End M ± SD (95% CI)		Start M ± SD (95% CI)	End M ± SD (95% CI)	
Weight (kg)	72.86 ± 8.91 (68.11–77.61)	70.82 ± 8.40 (66.34–75.30)	0.002	71.25 ± 7.30 (67.36–75.14)	69.71 ± 7.30 (65.82–73.60)	0.003	72.15 ± 8.64 (67.55–76.75)	72.47 ± 8.47 (67.96–76.98)	0.353
BMI (kg/m^2)	26.78 ± 1.55 (25.95–27.61)	26.03 ± 1.36 (25.31–26.75)	0.002	26.25 ± 1.37 (25.52–26.98)	25.66 ± 1.20 (25.02–26.30)	0.003	26.55 ± 1.96 (25.51–27.59)	26.67 ± 1.72 (25.75–27.59)	0.384
Percent body fat	25.94 ± 5.35 (23.09–28.79)	24.75 ± 5.20 (21.98–27.52)	0.001	25.94 ± 4.99 (23.28–28.60)	24.88 ± 4.99 (22.22–27.54)	0.002	25.88 ± 5.40 (23.00–28.76)	25.00 ± 5.52 (22.20–27.82)	0.014
HR (bpm)	76.94 ± 2.64 (75.53–78.35)	75.12 ± 3.63 (73.19–77.05)	0.031	74.62 ± 4.56 (72.19–77.05)	74.87 ± 4.50 (72.47–77.27)	0.752	76.19 ± 5.13 (73.46–78.92)	75.81 ± 4.10 (73.63–77.99)	0.549
SBP (mmHg)	129.12 ± 8.10 (124.80–133.44)	129.62 ± 6.74 (126.03–133.21)	0.843	131.00 ± 6.93 (127.31–134.69)	128.25 ± 6.40 (124.84–131.66)	0.221	125.62 ± 6.90 (121.94–129.30)	131.62 ± 9.33 (126.65–136.59)	0.031
DBP (mmHg)	81.75 ± 3.00 (80.15–83.35)	81.62 ± 3.28 (79.87–83.37)	0.926	81.62 ± 9.24 (76.70–86.54)	83.00 ± 3.58 (81.09–84.91)	0.239	82.62 ± 2.39 (82.35–84.89)	83.50 ± 4.23 (81.25–85.75)	0.379

Abbreviations: CI, confidence interval; HD, high dose green coffee extract; LD, low dose green coffee extract; PL, placebo; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; M, mean; SD, standard deviation.

significant for weight ($P < 0.001$), BMI ($P < 0.001$), and percent body fat ($P < 0.03$), indicating overall drug effects. This can be seen in Table 2, where there were improvements in weight, BMI, and percent body fat in the high-dose and low-dose arms, but not the placebo arm. For weight, the 2.04 ± 2.20 kg decrease in the high-dose arm was significant ($P < 0.003$), as was the 1.54 ± 1.74 kg decrease in the low-dose arm ($P < 0.005$); but the −0.34 ± 1.41 kg change in the placebo arm was not significant ($P = 0.355$). For BMI, the 0.74 ± 0.80 kg/m^2 decrease in the high-dose arm was significant ($P < 0.003$), as was the 0.58 ± 0.66 kg/m^2 decrease in the low-dose arm ($P < 0.004$); but the −0.12 ± 0.51 kg/m^2 change in the placebo arm was not significant ($P = 0.384$). For percent body fat, the 1.19% ± 1.22% decrease in the high-dose arm was significant ($P < 0.002$), as was the 1.06% ± 1.12% decrease in the low-dose arm ($P < 0.003$); surprisingly, the decrease was also significant in the placebo arm 0.88% ± 1.26% ($P = 0.015$). The sequence × time interaction was marginally nonsignificant for weight, ($P = 0.08$), was marginally significant for BMI ($P = 0.049$), and was significant for percent body fat ($P < 0.001$).

Most importantly, the triple interaction was significant for weight ($P < 0.001$) and BMI ($P < 0.001$), but not for percent body fat ($P = 0.239$). For weight, the 2.04 ± 2.20 kg decrease in the high-dose arm was greater than the 0.34 ± 1.41 kg increase in the placebo arm ($P < 0.013$), and the 1.54 ± 1.74 kg decrease in the low-dose arm was greater than the 0.34 ± 1.41 kg increase in the placebo arm ($P < 0.001$). The change in weight in the high-dose arm was not different from the change in weight in the low-dose arm ($P = 0.544$). For BMI, the 0.74 ± 0.80 kg/m^2 decrease in the high-dose arm was greater than the −0.12 ± 0.51 kg/m^2 change in the placebo arm ($P < 0.013$), and the 0.58 ± 0.66 kg/m^2 decrease in the low-dose arm was greater than the change in the placebo arm ($P < 0.002$). The change in BMI for the high-dose arm and low-dose arm did not differ ($P = 0.589$). A telephone interview was done 4 months post-trial, and 14 of the 16 subjects maintained their weight loss at the end of the study, while two subjects gained 1 kg and 0.75 kg.

Vital measures

Similar repeated-measures analysis of variance were performed on vital measures (heart rate, systolic blood

Table 3 Diet profile for 16 preobese subjects at beginning and during each arm of the study

Measurement time	Daily calorie intake (%) M ± SD	Daily carbohydrate intake (%) M ± SD	Daily fat intake (%) M ± SD	Daily protein intake (%) M ± SD	Binge eating incidence (n)
Beginning of study	2443.75 ± 260.69	58.75 ± 8.06	25.00 ± 9.66	16.25 ± 6.19	0
Arm 1	2406.25 ± 161.12	60.00 ± 6.32	24.38 ± 8.14	15.62 ± 6.29	0
Arm 2	2393.75 ± 161.12	61.25 ± 7.19	23.12 ± 10.14	15.62 ± 6.29	0
Arm 3 (end of study)	2418.75 ± 137.69	59.38 ± 6.80	25.00 ± 8.94	15.62 ± 6.29	0

Abbreviations: M, mean; SD, standard deviation.

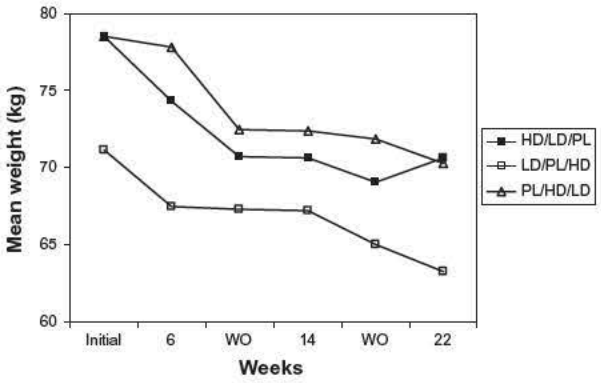

Figure 1 Mean weight changes over time for 16 subobese subjects.
Abbreviations: WO, washout; LD, low-dose; HD, high-dose; PL, placebo.

pressure, diastolic blood pressure). For heart rate, there was a marginally nonsignificant sequence effect ($P = 0.065$), and arm × time interaction ($P = 0.083$). The only significant result was a time effect ($P < 0.007$), reflecting an improvement between the beginning and end for each arm. No other effect was significant ($P > 0.165$). There were no significant results in the analysis of diastolic blood pressure ($P > 0.202$). For systolic blood pressure, there was a significant arm effect ($P < 0.005$), reflecting a surprising increase in systolic blood pressure across the three arms. There was also a marginally nonsignificant triple interaction ($P = 0.055$) versus 14 weeks.

All subjects completed the study and there were no side effects of using GCA. Regarding nutrient intake, there were no significant changes in calories, percentage carbohydrates, percentage fat, or percentage proteins at any time during the study. In looking at the individual effects of the GCA; 16 of 16 lost weight, 16/16 had decreased percent body fat 16/16 had a reduction in BMI, 3/13 experienced a decrease in systolic blood pressure, and 5/16 a reduction in diastolic blood pressure. Twelve of 16 had a decrease in heart rate. The decrease in heart rate of 2 beats per minute was significant but was of a lower magnitude than produced by a thermogenic combination of polyphenols, hesperidin, naringenin, and p-synephrine.[11] The lowest heart rate at the end of the study was 68 beats per minute. According to one of the cited study authors a decrease of 2 beats per minute is not clinically significant (H Preuss, personal communication) but is of benefit for heart health.

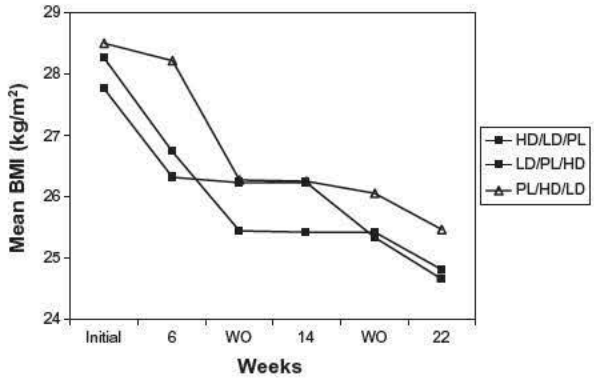

Figure 2 Mean BMI changes over time for 16 preobese subjects.
Abbreviations: WO, washout; LD, low-dose; HD, high-dose; PL, placebo.

Discussion

The mechanism(s) of the significant effects of GCA on weight loss, BMI, percent body fat, and heart rate are unknown. There have been some recent articles indicating that chlorogenic acid and its metabolite, caffeic acid, inhibit amylase at mM concentrations in vitro which, if it occurred in the gastrointestinal tract in vivo, would inhibit sugar absorption from starch consumption and thus decrease caloric input.[12] That chlorogenic acid has a significant influence on glucose metabolism was well demonstrated by Rodrigues de Sotillo et al when they were able to demonstrate a significant improvement in glucose tolerance in Zucker rats.[13] This relative deprivation of glucose could possibly explain the reduction in BMI as well as fat content seen in their other rat study[14] and in our human study. Another group has clearly demonstrated that chlorogenic acid may in fact have an antagonistic effect on human glucose transport.[15] Based on the dietary data in our study, the product was not an appetite suppressant. Extracts of green coffee beans inhibited pancreatic lipase in vitro with a 50% inhibitory concentration of 43 µM polyphenols.[16] In support of this result, caffeinated but not decaffeinated coffee supplementation in humans produced a decrease in lipoprotein lipase.[17]

Animal experiments have additionally demonstrated the effect of green coffee extract on fat metabolism, with chlorogenic acid alone having a moderate effect.[18] They were able to obtain significant data suggesting that chlorogenic acid not only retards the absorption of fats from the intestine but also activates fat metabolism in the liver. This was demonstrated by significantly lower levels of liver triglycerides after chlorogenic acid ingestion. A recent study in Japan found that coffee polyphenols enhance energy metabolism and reduce lipogenesis by downregulating sterol regulatory element-binding protein and similar molecules, which leads to the suppression of body fat accumulation.[19] Recently, intraperitoneal injection of chlorogenic acid to hamsters fed a high-fat diet caused an improvement in lipid profile, reduction in hepatic lipase, reduction in glucose and insulin and increased expression of peroxisome proliferator-

activated receptor. This is one of the key regulators of lipids and glucose.[20]

There have been a few human studies with green coffee extract. Thom investigated the efficacy and tolerability of a green coffee extract (Svetol®) added to instant coffee and compared within a randomized, placebo-controlled, double-blind study.[21] The product reduces the absorption of different types of sugar from the gastrointestinal tract. Forty obese volunteers were included in the 12-week study. Body weight, body composition, and blood pressure were recorded at baseline and every month during the study. The results show a significant difference in weight reduction in favor of the active group (5.4 kg versus 1.7 kg, a 4% decrease versus the placebo). BMI decreased 2.9% or 10%. There was a significant inhibitory effect of the product compared to glucose, and instant coffee, on glucose absorption in a glucose tolerance test. This same commercial product was investigated by another group.[22] The weight loss after 12 weeks was almost 5 kg in the treated groups and 2.5 kg in the placebo. A roasted and blended Arabica coffee rich in both green and roast bean constituents was tested in humans.[23] The coffee product caused a significant weight loss averaging 0.7 kg and a significant 5% loss of body fat along with a significant decrease in lymphocyte DNA damage. A meta-analysis of the three published and unpublished studies on these products concluded that the average weight loss of 2.5 kg was moderate and the results were promising.[26]

The results of our study are much more dramatic for weight loss and BMI than previous green coffee extract investigations. The subjects averaged slightly over an 8 kg weight loss which was more than 10% of the body weight. For our study 10 of 16 subjects showed at least a 10% weight loss; five of the remaining six showed at least 5% weight loss; and the last individual showed a 4% weight loss. The most remarkable result was the fact that all 16 of the subjects were classified as overweight at the beginning of the study and at the end six of the subjects were now in the normal BMI category, ie, a normal weight for their height. It must be said that the daily dose of GCA in this study ranged from 700 to 1050 mg and previous studies ranged from 180 to 200 mg/day.[24] There were no adverse effects in our study with the higher doses nor in the previous human studies according to the authors of the meta-analysis paper. It should not be overlooked that there was a slight (4.88 ± 11.24 mmHg) though nonsignificant increase in systolic blood pressure over the course of the study, which appears to be isolated to the placebo arm (see Table 2).

Other limitations were the small sample size of the study and the short washout periods between arms. Also, taking GCA three times per day in the high-dose arm and twice per day in the low-dose arm may have alerted subjects to dosage amount, at least in the low-dose arm. We do not believe sample size to have been a problem, given the linear crossover design of the study. This eliminates any possibility of the results reflecting a difference between groups, instead of between dosages. Also, all variables were objective measures, and follow-up showed that a majority of subjects (14 of 16) were able to maintain their lowered weight after the completion of the study.

Five drugs had been approved by the Food and Drug Administration, all of which exhibit weight loss. There are two currently approved for weight loss with sibutramine having been withdrawn from approval in 2011 due to tachycardia.[25] A recent review performed a meta-analysis of 30 trials of weight loss drugs of 1–4 years' duration, ie, 16 orlistat (n = 10,631 participants), 10 sibutramine (n = 2623), and four rimonabant (n = 6365). Attrition rates averaged 30%–40%. Compared with placebo, orlistat reduced weight by 2.9 kg (2.9%) sibutramine by 4.2 kg (4.3%), and rimonabant by 4.7 kg (4.1%). BMI reductions were 1.0 with orlistat and 1.5 with sibutramine. Lack of adherence to treatment seems to be a major factor limiting the efficacy and effectiveness of antiobesity drugs.[26] Thus the GCA with a weight loss of 8 kg (10.5%) and a BMI reduction of almost 3 makes the product superior to the prescription drugs. Weight loss of 5%–10% of initial body weight reduces cardiovascular and metabolic health risks associated with obesity.[27]

In a recent Israeli postmarketing study of over one million individuals, fewer than 2% completed 12 months of weight loss medication.[28] Those who continued for at least 4 months experienced a decrease in BMI of only 1 with a cost of $50–100 per month. GCA should provide an all natural, lower cost source as an effective therapy for overweight individuals. The efficacy for type 2 diabetics who have more coronary heart disease risk remains to be investigated.

Disclosure

The authors report no conflicts of interest in this work.

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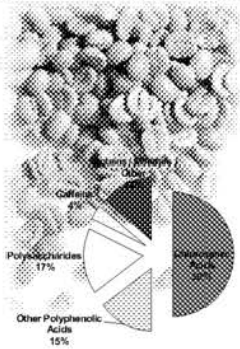
EXHIBIT B

Effect of Green Coffee Bean Extract (GCA), High in Chlorogenic Acids, on Glucose Metabolism, Dr. Nagendran MV

Abstract

Sixty healthy subjects (30m,30f) of Indian origin, in the age group of 20 – 40 yrs (Mean 29.9 yrs) and an average BMI of 21.6 were recruited into the study. Fifty six (27m,29f) completed all the study procedures. Following appropriate screening, all subjects underwent base line glucose tolerance tests followed by GTTs at appropriate intervals after consuming GCA in doses of 100, 200, 300 and 400 mg prior to a 100 gm oral Glucose challenge. The post GCA glucose tolerance tests clearly demonstrated significantly lower plasma sugars following similar glucose loads. The extent of blunting of plasma glucose following the glucose challenge ranged from 13.4% when they were given 100mg of GCA to 31.5% when they were given 400mg of GCA. The difference was statistically significant with a p=0.001. Our study clearly demonstrated that GCA has the ability to blunt the response of plasma sugar to a glucose load. We further believe that the degree of response could be dose dependent in the therapeutic range of GCA doses. Our findings are consistent with the work of other authors, although we believe this was the first study to measure plasma sugars following a Glucose challenge and ingestion of GCA



Study Design:

Subjects: Healthy adults, *n = 60,* Indian origin, age distribution 20 to 40 years

Method: 100 gram glucose charge

Measurements: Fasting glucose, SGOT, SGPT, OGTT, bilirubin, creatinine, urea

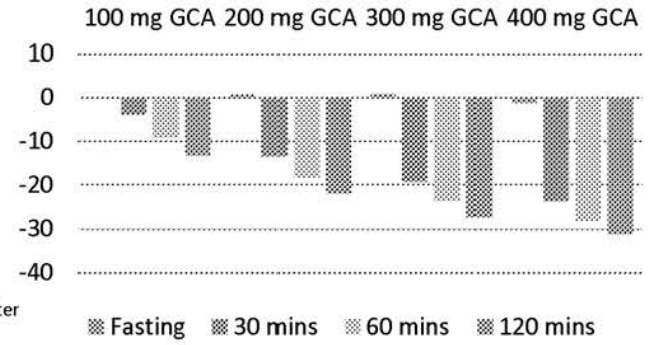
Active studied: Green Coffee Bean Extract, GCA®, standardized to 50% chlorogenic acids

Dosages of Active studied: 100, 200, 300, 400 milligrams

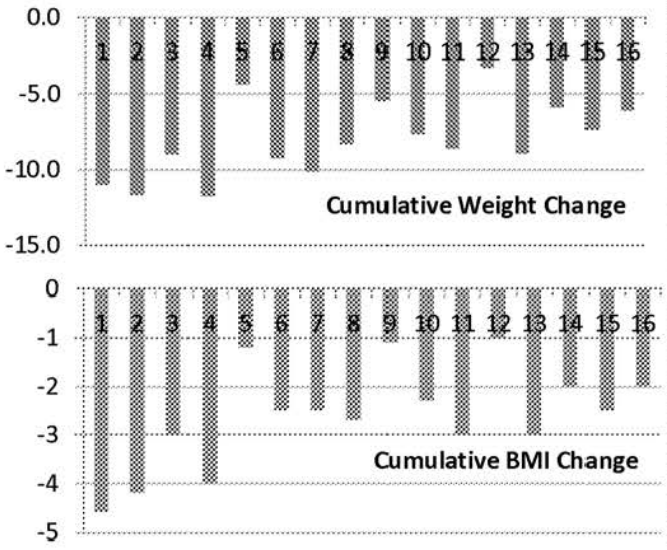
Results:

The percentage response of blood glucose load following an oral glucose challenge (1.3mg/kg) and GCA is a dose dependent phenomenon demonstrating a reduction between 13% to 32% within the range studied. GCA has potential as an all natural solution in assisting with blood glucose management. Given an ordinary meal the expected response could be even better

Percentage Reduction In Blood Sugar



Effect of Green Coffee Bean Extract (GCA), High in Chlorogenic Acids, on Body Composition, Dr. Nagendran MV



Abstract: A second study was completed on sixteen subjects with BMI values between 25 and 30 that were serially assigned to 3 groups of treatment with either low dose, high dose of green coffee bean extract (GCA) or a placebo. All subjects received each of the treatments for a period of six weeks. All subjects were screened to eliminate the possibility of independent factors influencing the study outcome. All subjects were assessed for weight change, BMI shift and body fat proportion every two weeks during the treatment period. The subjects had significant reduction in both weight and BMI during treatment with Low dose and High Dose GCA. We conclude that GCA when administered in doses used in this trial has a significant influence on weight, BMI and body fat proportion.

Study Design:

Subjects: Overweight adults, *n = 16,* Indian origin, age distribution 22 to 42 years

Method: Double Blind Placebo Cross Over Study

Measurements: Weight, BP, BMI, % Body Fat (bioimpedence analysis), Diet Intake

Active studied: Green Coffee Bean Extract, GCA®, 50% chlorogenic acids

Dosages of Active studied: 350 mg 2X /day & 350 mg 3X / day

Results: GCA may have the ability to manage and control the rate of glucose absorption for more efficient carbohydrate utilization in vivo and ultimately assist subjects with healthy weight management and carbohydrate metabolism. The overall men reduction in weight and BMI of the entire group was 10.6%.

GCA® provided by Applied Food Sciences Inc. Austin TX

Table 1. Characteristics at baseline and end of study, of 16 sub-obese subjects.

	Baseline	End of Study	Difference	
Characteristic	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*	Change
Weight (kg)	76.69 ± 7.91	68.65 ± 7.78	8.04 ± 2.31**	-10.5%
BMI (kg/m^2)	28.22 ± 0.91	25.25 ± 1.19	2.92 ± 0.85**	-10.3%
BIA	28.13 ± 4.95	23.69 ± 4.95	4.44 ± 2.00**	-15.8%

Note. BMI = Body Mass Index; BIA = Bioelectrical Impedance Analysis; ** $p < .0001$,

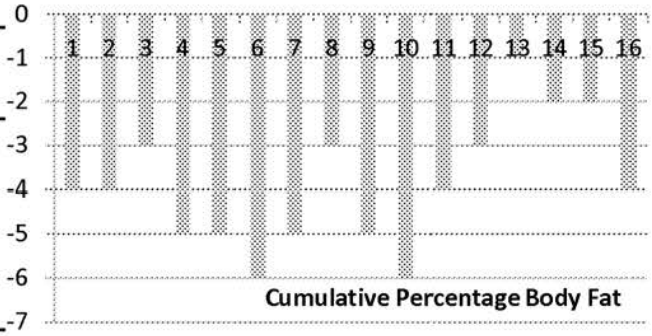


EXHIBIT C

Green Coffee Bean Extract GCA® from Applied Food Sciences Inc. Proven in Randomized, Double Blind, Placebo-controlled Study to Efficiently Aid Weight Loss Lower Body Mass

Adult weight gain and obesity have become worldwide problems. Issues of cost and potential side effects of prescription weight loss drugs have led overweight and obese adults to try nutraceuticals that may aid weight loss. One promising nutraceutical provided by Applied Food Sciences, Inc. out of Austin, TX is green coffee bean extract, or GCA®, which contains high concentrations of chlorogenic acids that are known to have health benefits and to influence glucose and fat metabolism. A 22-week crossover study was conducted to examine the efficacy and safety of a commercial green coffee bean GCA® at aiding weight loss and lowering body mass in 16 overweight adults.

AFS Logo

"Significant reductions were observed in body weight (−8.04 ± 2.31 kg), body mass index (−2.92 ± 0.85 kg/m2), and percent body fat (−4.44% ± 2.00%), as well as a small decrease in heart rate (−2.56 ± 2.85 beats per minute)"

Bangalore, India (PRWEB) February 02, 2012

The World Health Organization predicts there will be 2.3 billion overweight adults in the world by 2015, and more than 700 million of them will be obese.

Worldwide obesity has more than doubled since 1980. In 2008, 1.5 billion adults, 20 years of age and older, were overweight (World Health Organization (WHO). Fact Sheet 311. Geneva: WHO; 2011).

With the high cost of prescription weight loss drugs and the fear of side effects, the general public is turning to nutraceuticals. One promising nutraceutical provided by Applied Food Sciences, Inc. out of Austin, TX is green coffee extract, which contains high concentrations of chlorogenic acids that are known to have health benefits and to influence glucose and fat metabolism.

A 22-week crossover study was conducted to examine the efficacy and safety of a commercial green coffee extract product GCA® at reducing weight and body mass in 16 overweight adults. The green coffee extract utilized for this study was provided by Applied Food Sciences Inc (Austin, TX) under the trade name GCA®. This was a randomized, double-blind, 22-week study that implemented a crossover design to compare a low-dose green coffee extract, a high-dose green coffee extract, and a placebo. The results of the study were statistically significant reductions in weight, BMI, percent body fat, and heart rate after consuming GCA for two-thirds of the 22-week crossover study. All subjects completed the study and there were no side effects of using GCA.

Regarding nutrient intake, there were no significant changes in calories, percentage carbohydrates, percentage fat, or percentage proteins at any time during the study. In looking at the individual effects of the GCA; 16 of 16 lost weight, 16/16 had decreased percent body fat 16/16 had a reduction in BMI, 3/13 experienced a decrease in systolic blood pressure, and 5/16 a reduction in diastolic blood pressure. The results of the study are much more dramatic for weight loss and BMI than previous green coffee extract investigations.

The subjects averaged slightly over an 8 kg weight loss which was more than 10% of the body weight. For the study 10 of 16 subjects showed at least a 10% weight loss; five of the remaining six showed at least 5% weight loss; and the last individual showed a 4% weight loss. The most remarkable result was the fact that all 16 of the subjects were classified as overweight at the beginning of the study and at the end six of the subjects were now in the normal BMI category, ie, a normal weight for their height. Subjects were examined individually at Trinity Hospital, Bangalore, India.

To read entire study - click on attached pdf article.

Applied Food Sciences (AFS) specializes in the development and marketing of proprietary technologies used in foods, beverages and nutritional supplements. AFS's revolutionary products have been featured on television and in publications such as CNN, NBC, USA Today, Parade, Muscle and Fitness, FLEX, Prevention and Newsweek.

For more information on AFS visit their website or call customer service at 1-800-345-9666.

EXHIBIT D

Dr. Joe Vinson to Speak at ACS National Meeting & Expo on Applied Food Sciences' Green Coffee Extract GCA™ as a Weight Management Tool in the Reduction of Body Mass

Well known antioxidant expert Dr. Joe Vinson is presenting at the ACS National Meeting and Expo in San Diego on March 27, at 9:50 a.m. This talk comes shortly after the clinical study demonstrating Applied Food Sciences' GCA™, green coffee bean extract, was shown to aid in effective weight management and lower total body mass when controlling diet and exercise.

GCA logo

(PRWEB) March 07, 2012

Applied Food Sciences' green coffee bean extract, GCA™, is a functional ingredient derived from unroasted coffee beans. It's 100% natural and has been linked to both heart health and assisting with optimum blood glucose management. Most recently in a randomized double blind placebo-controlled crossover study GCA™ was proven to aid in weight loss when combined with controlling diet and exercise. On Tuesday March, 27 at 9:50 am PST, Dr. Joe Vinson, Professor at the University of Scranton, will provide a presentation on the results of the GCA™ clinical study at the ACS National Meeting and Exposition in San Diego, CA., Embassy Suites Hotel, Monterey Ballroom I.

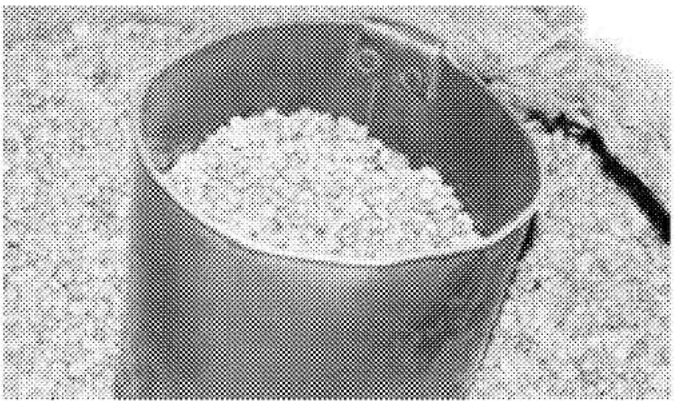
The presentation will review how obesity is a growing epidemic in industrialized societies. Overweight and obese subjects in the US now account for 68% of the population. There are prescription drugs for weight loss available however the concern over side effects cause large dropout rates in clinical studies and lack of overall long term compliance. The data presented by Dr. Vinson will demonstrate the effectiveness of GCA™ in several key health biomarkers including body weight, body mass index (BMI), fat mass (BIA), heart rate and blood pressure. For dieticians assisting clients in healthy weight management and those wanting to lead a healthy lifestyle, GCA™ can be a safe, effective, and inexpensive nutritional product to add to their current regimen.

Recent peer review of the data was also presented at the World Diabetes Congress Dubai 2011 in December 2011, 6th Annual Obesity Summit: Science and Practice of Obesity Management Cleveland Clinic in October 2011 Cleveland, Ohio, and Obesity 2011: The 29th Annual Scientific Meeting of the Obesity Society October 2011 Orlando, FL. For more information regarding this and other studies visit http://www.appliedfoods.com or click on the attached article. Applied Food Sciences, Inc. is an Austin, TX based company.

EXHIBIT E

Dr. Oz Show Highlights GCA® Green Coffee Bean Extract from Applied Food Sciences Inc., Proven in Recent Human Study to Lower Body Mass Index and Aid in Weight Management

After a ground breaking study was presented at the American Chemical Society Meeting in San Diego (March 2012) green coffee bean extract is becoming all the buzz in weight management products. With staggering results participants in the study lost an average of 10% of their body weight without changing diet or exercise. This phenomenal green coffee extract GCA® from Applied Food Sciences was highlighted on the Dr. Oz show.



Green (unroasted) coffee beans

"Subjects that took part in a 22 week double blind placebo cross over study lost an average of 10% of their total body weight without changing their diet or exercise habits"

(PRWEB) May 09, 2012

After a ground breaking study was presented at the American Chemical Society Meeting in San Diego (March 2012), green coffee bean extract is becoming all the buzz in weight management products. As seen on the Dr. OZ show, green coffee extract regulates the body's ability to break down glucose or carbohydrates, ultimately helping the body burn fat. Subjects that took part in a 22 week double blind placebo cross over study lost an average of 10% of their total body weight without changing their diet or exercise habits† (Randomized, double-blind, placebo-controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2012:5 21–27). However, what people don't know is that not all green coffee bean extracts will have the same functional effect aiding in weight management in the body. The green coffee extract that was used in the actual study was patent pending GCA®, manufactured by Applied Food Sciences, Inc. (AFS), derived from the highest quality unroasted coffee beans. It is important to note that AFS sources it's green coffee beans directly from farmers using sustainable and socially responsible practices. This ensures only high quality pure green beans are used to make GCA®.

"The quality and polyphenol profile of green coffee extract is very significant", states Loretta Zapp CEO at AFS. "Our scientists know how to perfectly harmonize science and nature so when extracting the green coffee beans we ensure that the beneficial compounds are present in the correct ratios to produce only the highest quality product." The GCA® green coffee extract and weight management study have already made waves in major print publications and now is getting attention on a national television circuit as highlighted on the Dr. Oz show. "Because all plants are complex entities, it's critical to control and monitor the composition of the extract in order to achieve the desired function in the body", continues Loretta Zapp. "AFS has clinically proven the efficacy of its GCA® green coffee extract yielding the best results and providing synergistic effects for optimum product performance. Not all green coffee extracts have such scientifically proven data attached."

Applied Food Sciences Inc. is a health and wellness company dedicated to providing nutritional solutions to the food and beverage industries. Combining research collaborations, state of the art processing partners, and natural plant based raw material integration allows Applied Food Sciences to bring innovative, high quality, research driven products into the marketplace. To learn more about the science behind GCA®, green coffee extract, or some of AFS' other functional ingredients, technologies or consumer product solutions please visit us at http://www.appliedfoods.com or call 1-800-345-9666 or email: aminton(at)appliedfoods(dot)com.

† See attached study for complete results.