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Hypolipemic Effect of *Garcinia cambogia* in Obese Women

Carlos A. R. Vasques,* Ricardo Schneider, Luiz C. Klein-Júnior, Andressa Falavigna, Ivone Piazza and Simone Rossetto

Grupo de pesquisa em saúde humana e ambiente, Instituto de Ciências da Saúde, Universidade Feevale, RS-239, 2755, 93352-000, Novo Hamburgo, Rio Grande do Sul, Brasil

Garcinia cambogia **seems to promote weight reduction and improvement on lipid profile by its major compound, hydroxycitric acid (HCA), blocking ATP-citratelyase, potentially inhibiting lipogenesis. Furthermore, it is suggested that its extract is able to change the adipokine levels. Thus, the aim of this study was to analyse the effect of *G. cambogia* on the lipid profile, endocrine, calorimetric and anthropometric parameters of obese women. The women (BMI > 25 kg/m^2; age 25–60 years), divided in treated ($n = 30$) and control ($n = 13$) groups, received 2.4 g (800 mg 3×/day) of garcinia extract (50% of HCA) or placebo during 60 days, respectively, as well as dietary control. Weight, BMI, waist–hip ratio and percentage of fat mass, resting metabolic rate, respiratory coefficient, triglycerides (TG), total cholesterol, HDL and LDL, leptin and insulin serum levels were evaluated. TG was significantly reduced in the treated group ($p = 0.0002$) and the post-treatment variation was different compared to the placebo group ($p = 0.04$). No significant response was observed on other variables of the lipid profile, or on the anthropometric and calorimetric parameters. Leptin and insulin levels did not change significantly after the treatment. The short-term treatment with *G. cambogia* demonstrated a hypotriglyceridemic effect, which does not appear to be related to changes in leptinemia. Copyright © 2013 John Wiley & Sons, Ltd.**

Keywords: Garcinia cambogia; leptin; lipid profile; obesity.

INTRODUCTION

Obesity is defined as an accumulation of body fat resulting from an energy imbalance primarily produced by excessive caloric intake and/or physical inactivity. Excess of body fat is a known risk factor for metabolic disorders, including dyslipidemia and type 2 diabetes. In addition to environmental factors, obesity and its comorbidities may be associated with endocrine factors, such as insulin and adipokines, which are related to endogenous mechanisms of energy homeostasis (Ahima *et al*., 2006).

Leptin is an adipokine that acts on the hypothalamus, inducing satiety and thermogenesis (Ahima and Lazar, 2008). Insulin acts on the central nervous system similarly to leptin, stimulating receptors on the neurons of the hypothalamic arcuate nucleus and inducing satiety by the same signaling pathway (Niswender *et al*., 2004). Thus, the mechanisms of resistance to these hormones and consequent changes on their secretion profiles appear to be closely associated with the pathophysiology of obesity and its metabolic comorbidities.

The current pharmacological treatment of obesity involves primarily the promotion of weight reduction, without a direct influence on the metabolic disorders related to the accumulation of body fat. In general, pharmacotherapy of obesity is supported by the use of anorectic agents such as sibutramine and other psychostimulants, which can promote many undesirable effects, such as cardiovascular disorders, anxiety and addiction. In contrast, some natural products, like the one obtained from *Garcinia cambogia* Desr. (Guttiferae), can be an alternative to control and reduce body weight by acting peripherally on the metabolic profile, without interfering with the activity of the central nervous system. The standardized extract of *G. cambogia* has hydroxycitric acid (HCA) as major constituent. This compound is a competitive inhibitor of ATP-citrate lyase, a cytosolic enzyme that catalyses the cleavage of citrate into oxaloacetate and acetyl-CoA, which could inhibit the endogenous lipogenic activity (Sullivan *et al*., 1977).

Studies in animal models have shown that HCA has the ability to promote oxidation of fatty acids and to improve the lipid profile (Ishirara *et al*., 2000; Hayamizu *et al*., 2003). It is also observed that Garcinia extract may reduce leptin and insulin levels in animals previously treated with high-fat diet (Hayamizu *et al*., 2003; Kim *et al*., 2008). In clinical studies, Mattes and Bormann (2000) found a reduction in body weight in obese patients after treatment with extract of Garcinia, which was not observed in the study of Heymsfield *et al.* (1998). More recently, Vasques *et al.* (2008) identified a hypolipemic effect in obese subjects treated with a combination of extracts of *G. cambogia* and *Amorphophallus konjak* fibers (glucomannan), but there were no significant changes in anthropometric and calorimetric parameters. In addition, Kim *et al.* (2011) did not observe the ability of the extract of *G. cambogia* to reduce body weight in obese subjects, but founded a cardiovascular protective effect from the increased HDL-cholesterol.

* Correspondence to: C.A.R. Vasques, Pró-reitoria de Pesquisa, Universidade Feevale, RS-239, 2755, 93352–000,Novo Hamburgo, RS, Brazil.
E-mail: carlosrv@feevale.br

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In fact, despite the probable action of the HCA on lipid metabolism, few clinical studies evaluated the ability of *G. cambogia* extract in the improvement of the lipid profile or its possible effects in changing the leptin levels in humans. Thus, considering that studies have indicated the correlation of levels of leptin and metabolic changes, both in animals and humans (Asensio *et al.*, 2004; Soderberg *et al.*, 2009), it is possible that the hypolipemic effect promoted by the extract of garcinia is related to its ability to induce changes in the leptin secretion. In this sense, the present study aimed to evaluate the clinical efficiency of the treatment with the extract of *G. cambogia* on the improvement of anthropometric and metabolic parameters in obese women, as well as analyse its influence on leptin levels.

METHOD

Subjects. Of the 60 women selected in the city of Novo Hamburgo - Brazil, 43 completed the trials. All were overweight (BMI $\geq$ 25 kg/m2), aged between 25 and 60 years old and met the following inclusion criteria: stable eating habits; not following a low-calorie diet; stable body weight (variation of less than 4 kg) over the last three months; stable level of physical activity over the last six months; no use of drugs which might significantly affect weight, appetite, lipid profile or blood glucose levels, over the eight weeks prior to the start of the study; good general state of health. Subjects with the following pathologies, history or current clinical status were excluded: pregnancy or lactation, stopped smoking during the last six months, gastroplasty or any other gastrointestinal weight-reducing surgery, chronic kidney disease, history of recurrent kidney stones, liver dysfunction, insulin-dependent diabetes, drug-controlled type 2 diabetes, untreated high blood pressure, active gastrointestinal dysfunction, history or symptoms of gallstones, cancer, history of endocrine disorders (particularly hypothyroidism), history of bulimia and/or laxative abuse, mental disorders with impaired independence, history of alcohol or other drugs abuse. Subjects were additionally required to meet the following clinical criteria: creatinine clearance of 75–115 mL/min; alkaline phosphatase levels no higher than 300 U/I; aspartate aminotransferase (AST) levels from 12 to 46 U/l (37°C); alanine aminotransferase (ALT) levels from 3 to 50 U/l (37°C); thyrotropin (TSH) levels from 0.3 to 5.0 μUI/mL.

Study design. This was a double-blind randomized study to evaluate the pharmacotherapeutic efficacy of 60 days treatment with daily doses of *G. cambogia* standardized extract (2.4 g/d). The sample was randomly divided in the treatment group ($n = 30$) and control ($n = 13$), which received capsules containing 800 mg of *G. cambogia* (50% HCA) or placebo, respectively. All subjects were instructed to take one capsule three times a day, roughly 30 min before each main meal (breakfast, lunch and dinner). The volunteers were advised to maintain constant levels of physical activity. After prior assessment of daily caloric intake (1903 ±453 kcal/d), all subjects received an individualized diet during treatment, with an average reduction to 1523 ±185 kcal/d. Immediately before and after 60 days of treatment, the following parameters were evaluated: anthropometric measurements, resting energy expenditure, lipid profile, fasting glucose and serum determination of insulin and leptin. Acute toxicity was assessed by analysis of hepatic transaminases and creatinine clearance, and recording of adverse symptoms reported during the treatment. The study protocol complied with the bioethical principles established in the Declaration of Helsinki, and was approved by the Research Ethics Committee at the Universidade Feevale, Brazil. Informed consent to participation and confidential use of data was given by all subjects.

Measurements. *Patient reporting and nutritional assessment.* Clinical, nutritional and pharmacotherapeutic data were obtained by patient reporting. The data obtained were used for sample selection, and to monitor possible adverse effects during phytotherapy, changes in physical activity in the course of the study, and use of any drugs or onset of any illness which might influence results. To estimate the usual caloric intake of the participants during the pre-treatment, a food diary of three days was used, randomly chosen within the week. Caloric intake (kcal/d) was evaluated by the arithmetic mean of the record of three days, and the data analysed with the Win Clinic Diet® 3.0 software package (Brubins Ltda.). Over the 60 days of treatment, the subjects received individualized diets which aimed to reduce an average of 500 kcal/d.

Weight, height and circumferences. In accordance with the protocol developed by the International Society for Advancement in Kinanthropometry, body mass (BM), height, waist circumference (WC) and hip circumference (maximum gluteal girth) were measured. Subjects were weighed on a Filizola® balance (accurate to 100g), height was measured using a Sayol® stadiometer (accurate to 0.1 cm) and circumferences were measured with a Fanny® tape measure (accurate to 0.1 cm). These data were used to calculate the body mass index (BMI) and waist:hip ratio (WHR).

Estimation of body composition. Two-compartment body composition, fat mass (FM) and free fat mass (FFM) were measured by tetrapolar bioelectrical impedance analysis in 12-h-fasted subjects on a restricted physical-activity schedule, using a Bodystat/1500® analyser, operating at 50 KHz. FFM was assessed using the equation developed by Deurenberg *et al.* (1999): $\text{FFM (kg)} = 0.340(h^2/R) + 0.1534(h) + 0.273(BM) - 0.127(age) - 12.44$, where: h = height (cm), R = resistance (Ohmns). FM was obtained from the difference between BM and FFM, and presented as percentage (% FM).

Resting energy expenditure. Resting energy expenditure (REE) was assessed by indirect calorimetry, using a TEEM 100® (INBRASPORT) calorimeter: 12-h-fasted subjects on a restricted exercise schedule lay comfortably on their backs in a silent room at a mean temperature of 24° ±1°C, and VO_2 and VCO_2 were recorded over a 15-min period; data obtained over the last 10 min were used to calculate REE. REE estimation was based on the Weir (1949) equation: $\text{REE (Kcal/min)} = [3.9(VO_2) + 1.1(VCO_2)]$. The value obtained was multiplied by 1440 in order to estimate REE for 24 h. REE was also calculated by the relationship with BM (kcal/kg/24 h). Additionally, mean values for the respiratory quotient (RQ) were also obtained.

Laboratory tests. Blood samples were collected in accordance with the clinical routine protocol. Fasting blood glucose (GLU), total cholesterol (TC), HDL-cholesterol (HDL-c) and triglyceride (TG) levels were measured using a colorimetric enzyme assay method (CEPA® kits - MBiolog Diagnósticos Ltda); LDL-cholesterol (LDL-c) levels were estimated using the equation developed by Friedewald *et al.* (1972): LDL-c = TC – (HDL-c + TRI/5), for [TG] < 400 mg/dL. Serum levels of leptin were determined by Enzyme-Linked Immunosorbent Assay using LINCO® kits (human leptin ELISA kits). Insulin levels and TSH were analysed by indirect Chemiluminescence (Beckman-Coulter® kits). In order to identify possible liver or kidney injury in the course of treatment, serum transaminase (AST and ALT) and creatinine levels were also measured. Creatinine clearance was estimated using Cockroft and Gault's equation (1976).

Production and dispensing of phytomedicines. The production of the phytomedicine used in this study was conducted in School of Pharmacy, Feevale University (Novo Hamburgo-RS, Brazil). The phytomedicine was presented in the form of capsules containing 800 mg of standardized extract of G. cambogia acquired from Henrifarma Chemicals and Pharmaceuticals LTD under the lot number 6130601 SH. The chemical marker HCA concentration was 51.02%, as determined by HPLC analysis. Capsules of the same size and color were used for the phytomedicine and for the production of placebo. The excipient used was a mixture of corn starch (98.5%), magnesium stearate (0.5%) and colloidal silicon dioxide (1%). Placebo capsules were supplemented with excipient only. The capsules were stored in bottles of 180 units and dispensed immediately after the pre-treatment assessments. All subjects were instructed to ingest one capsule three times daily approximately 30 min before their main meals. The compliance of the use of the medication was monitored by counting the capsules remaining at the end of the 60 days of treatment.

Statistical analysis. Results are shown as means ± standard deviation. The Kolmogorov–Smirnov test was applied to test for a normal distribution of variables. Differences between means were analysed using Student's *t*-test; values of $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS statistical analysis software.

RESULTS

During treatment, there were no significant changes in liver transaminase levels and values of creatinine clearance. Potential treatment-related adverse reactions reported by subjects are shown in Table 1.

At the end of treatment, no changes were observed on anthropometric and calorimetric parameters, and no significant differences were found between mean values of the control and treated groups for these variables (Table 2).

As summarized in Table 3, the treatment induced no significant variation on HDL-c, LDL and COL-T-c. However, the TG mean of the treated group after 60 days (109.52 ± 38.7 mg/dL) was significantly lower than the pre-treatment (132.35 ± 41.61 mg/dL, $p = 0.0002$). As illustrated in Fig. 1, after the treatment was observed an average reduction of −22.9 ± 5.34 mg/dL ($p = 0.04$) for the treated group, demonstrating a significant hypotriglyceridemic effect compared to placebo (4.53 ± 33.4 mg/dL).

DISCUSSION

The results obtained in this study suggest that short-term treatment with the standardized extract of *Garcinia cambogia* showed a significant hypotriglyceridemic effect influencing neither anthropometric and calorimetric parameters nor leptin or insulin serum levels. The treatment also did not affect cholesterol serum levels.

Although some studies suggest the ability of *G. cambogia* extract to reduce body weight (Mattes and Bormann, 2000), the present study did not demonstrate improvement in any of the anthropometric parameters analysed. This result corroborates with those observed by Heymsfield *et al.* (1998), where a hypocaloric diet plus garcinia extract (90 days) was not able to reduce body weight compared to placebo.

A study using animal models found that chronic treatment with the *G. cambogia* extract may display endocrine effects. In rodents, Hayamizu *et al.* (2003) found a reduction in leptin and insulin serum levels after a 4 week treatment with garcinia extract. It could explain our findings regarding the effect of the extract on TG levels; however, this effect was not observed in the present study. In the tested dose, the hypotriglyceridemic effect was characterized by a decrease of approximately 28% of TG levels. Thus, this effect seems to have been promoted directly through the basic mechanism of action of HCA on the synthesis of fatty acids, and not indirectly through changes in leptin levels that remained stable during treatment.

The major compound of the extract of *G. cambogia*, HCA, is an inhibitor of ATP-citrate lyase (Sullivan *et al.*, 1977) and therefore may reduce the biosynthesis of fatty acids. Whereas the extract was administered before meals, its absorption and distribution coincide with the absorptive state. Therefore, pharmacological inhibition of lipogenesis can contribute to the hypotriglyceridemic effect observed.

Table 1. Adverse symptoms reported by subjects during the treatment

Group	Symptoms	Frequency (n)
Placebo	Gastric discomfort	7.6% (1)
	Durst	7.6% (1)
	Diuresis	7.6% (1)
	Constipation	7.6% (1)
	Increased evacuation	7.6% (1)
Treated	Gastric discomfort	9.6% (3)
	Durst	6.4% (2)
	Increased evacuation	6.4% (2)
	Nausea	6.4% (2)
	Constipation	3.2% (1)
	Dizziness	3.2% (1)
	Diuresis	3.2% (1)

Table 2. Antropometric and calorimetric parameters before and after 60 days of treatment

	Pre-treatment		60 days		Variation	
	Placebo	Treated	Placebo	Treated	Placebo	Treated
BMI (kg/m^2)	32.69 ± 4.18	33.81 ± 5.5	31.79 ± 3.46	34 ± 5.6	−0.24 ± 0.87	0.17 ± 0.56
FFM (kg)	50.49 ± 6.57	47.61 ± 4.43	49.93 ± 8.45	48.30 ± 4.98	−0.72 ± 3.52	0.41 ± 1.76
%FM	41.30 ± 6.3	44.49 ± 5.39	40.94 ± 7.73	44.5 ± 5.47	0.21 ± 4.15	−0.12 ± 5.4
WHR	0.81 ± 0.05	0.82 ± 0.09	0.80 ± 0.07	0.82 ± 0.09	−0.01 ± 0.03	0 ± 0.03
REE (Kcal/Kg/24h)	17.73 ± 2.76	19.73 ± 6.87	18.89 ± 0.96	17.74 ± 4.64	1.16 ± 2.56	−1.57 ± 7.0
RQ	0.90 ± 0.09	0.86 ± 0.13	0.93 ± 0.14	0.82 ± 0.08	0.03 ± 0.15	−0.03 ± 0.2

BMI = Body mass index. FFM = Free Fat Mass. %FM = Fat mass percentage. WHR = waist/hip ratio. REE = Resting energy expenditure. RQ = respiratory quotient. Data are expressed as means ± SD.

Table 3. Endocrine and metabolic variables before and after 60 days of treatment

	Pre-treatment		60 days		Variation	
	Placebo	Treated	Placebo	Treated	Placebo	Treated
T-COL	169.31 ± 24.48	188.45 ± 30.14	161.38 ± 37.29	180.10 ± 38.71	−7.36 ± 20.9	−8.1 ± 28.5
LDL-c	102.20 ± 19.44	115.75 ± 27.73	91.85 ± 30.29	109.77 ± 37.84	−9.61 ± 19	−5.28 ± 27.5
HDL-c	42.69 ± 9.52	46.19 ± 13.43	44.15 ± 8.86	48.50 ± 12.86	1.27 ± 6.6	1.59 ± 8.4
TG	121.85 ± 69.17	132.35 ± 41.61	127.08 ± 73.28	109.52 ± 38.7 [b]	4.53 ± 33.4	−22.9 ± 5.3 [a]
Insulin	9.36 ± 4.23	12.16 ± 7.64	9.05 ± 4.37	12.35 ± 8.32	−0.21 ± 3.16	0.47 ± 3.53
Leptin	43.89 ± 16.62	39.26 ± 16.04	40.66 ± 18.14	37.22 ± 14.97	−3.22 ± 15.4	−2.04 ± 9.08

T-COL = Total cholesterol. LDL-c = LDL cholesterol. HDL-c = HDL cholesterol. TG = Triglycerides. Data are expressed as mean ± SD. [a] $p = 0.04$; [b] $p = 0.0002$. *t*-test for independent samples (placebo group × treated group) and paired *t*-test (before treatment × after treatment).

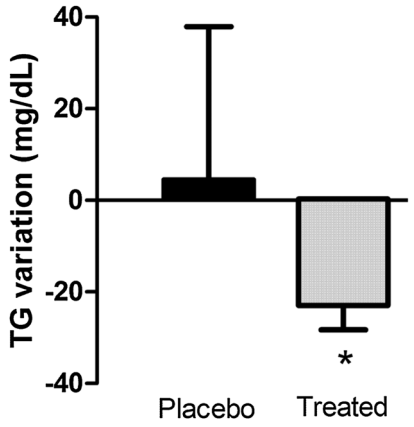

Figure 1. TG variations after 60 days of treatment. *$p < 0.05$.

In fact, a reduction of lipogenesis could result in calorimetric changes due to possible variations in RQ, reflecting a variation of the lipid oxidation level. In the study of Vasques *et al*. (2008), which also evaluated the effect of the extract on the RQ and resting metabolic rate in humans, changes in these calorimetric variables were not observed. In rodents, Ishihara *et al*. (2000) found a decrease in respiratory quotient in animals treated with *G. cambogia* (HCA 10 mg/day) orally for 25 days, indicating that the extract may promote increase of the lipid oxidation. However, in the present study, such change was not detected.

The treatment does not seem to promote acute toxicity, once the markers of hepatic lesions (AST and ALT) and renal function (creatinine) remained stable during normal use of the extract. Furthermore, the adverse symptoms reported by research subjects do not seem to be related to the treatment.

In conclusion, our results reinforce the fact that the extract does not seem to have an effect on anthropometric and calorimetric parameters. Further studies should be conducted to better describe the pharmacodynamic and pharmacokinetic properties of the standardized extract of *Garcinia cambogia*. The active constituent of this extract seems to inhibit the biosynthesis of lipids, promoting a hypotriglyceridemic effect independently of changes in leptin and insulin serum levels. This effect should be further detailed by other clinical trials in order to establish a possible benefit of this herbal extract for the treatment of dyslipidemia associated with obesity.

Conflict of Interest

The authors declare that they have no conflict of interest.

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