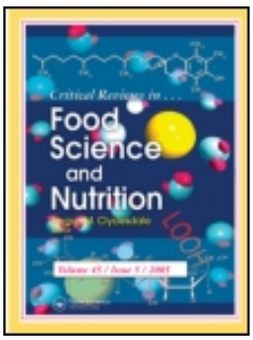

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Evaluation of the Safety and Efficacy of Hydroxycitric Acid or *Garcinia cambogia* Extracts in Humans

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Several studies have shown that Garcinia cambogia plays an important role in the regulation of endogenous lipid biosynthesis. This effect is specially attributed to (-)-hydroxycitric acid (HCA) inhibiting the enzyme ATP-dependent citrate lyase, which catalyzes the cleavage of citrate to oxaloacetate and acetyl-CoA. Although several studies have found that the administration of G. cambogia extracts is associated with body weight and fat loss in both experimental animals and humans, we should be cautious when interpreting the results as other randomized, placebo-controlled clinical trials have not reported the same outcomes. Furthermore, most studies in humans have been conducted on small samples and mainly in the short term. None of them have shown whether these effects persist beyond 12 weeks of intervention. Therefore, there is still little evidence to support the potential effectiveness and long-term benefits of G. cambogia extracts. With regard to toxicity and safety, it is important to note that except in rare cases, studies conducted in experimental animals have not reported increased mortality or significant toxicity. Furthermore, at the doses usually administered, no differences have been reported in terms of side effects or adverse events (those studied) in humans between individuals treated with G. cambogia *and controls.*

Keywords *Garcinia cambogia*, body weight, lipid profile, safety

INTRODUCTION

Garcinia cambogia, also known as *Malabar tamarind*, originates in Southeast Asia and is a small to medium-sized tree of the *Guttiferae* family, of which over 180 species are known. These are distributed throughout Asia, Africa, and the Polynesian islands (30 of them in India). Its fruit, of approximately 5 cm in diameter, has been used for centuries (particularly in East India) for culinary and therapeutic purposes. Tamarind extracts have been used to enhance the flavor of food such as meat, shellfish, and some beverages and even as preservative for fish. It has also traditionally been used to achieve a feeling of satiety after eating, and even for some bowel disorders due its possible bacteriostatic effect (due to its low pH) and, in veterinary medicine, for mouth diseases in livestock. The fruit pulp and rind (a small reddish-yellow ovoid pumpkin) have traditionally been the most commonly used parts for therapeutic purposes, as they contain high amounts of (-)-hydroxycitric acid (HCA), one of the components to which beneficial effects have been attributed as reported in several different studies on body weight regulation.

The dried fruit contains approximately 10 to 30% citric acid, most of which is HCA, whose structure is almost identical to citric acid (Lewis and Neelekantan, 1965). HCA has 4 isomeric forms: (-)-HCA, (+)-HCA, (+)-allo-HCA and (-)-allo-HCA (see Figs. 1 a-d, respectively). (-)-HCA is the main acid found in the fruit of *G. cambogia*. Although HCA can be isolated through different methods in its free form, as a calcium or potassium salt or as lactone, natural tamarind extracts are currently marketed as calcium/potassium salts of (-)-HCA (HCA-SX), containing approximately 60% HCA.

ACTION MECHANISMS, EFFICACY, AND TOXICITY STUDIES

There are several published studies investigating the action mechanisms that might explain the possible beneficial effects

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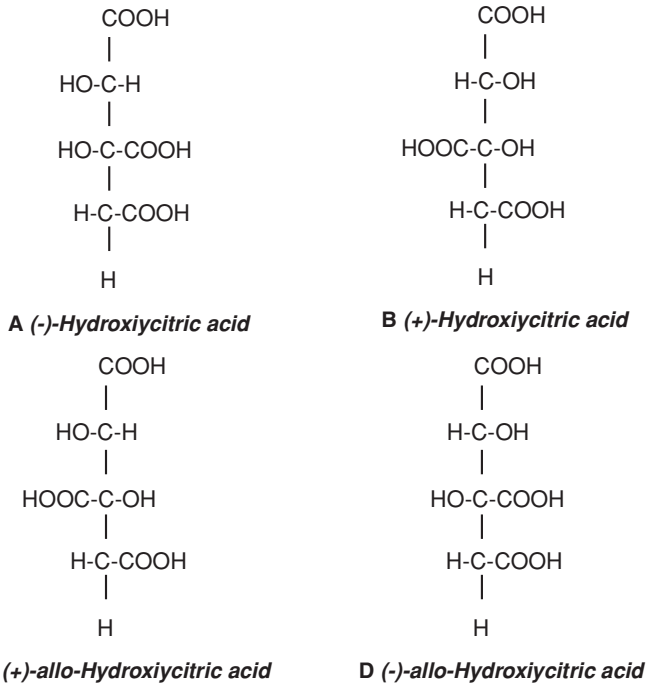

Figure 1 Chemical structures of stereoisomers of hydroxycitric acid.

associated with the intake of HCA, particularly in relation to body weight. Several studies on humans have also been conducted in order to evaluate its efficacy in different situations and the safety of its ingestion. However, one of the main difficulties in evaluating the efficacy and toxicity of HCA is that, in many of the studies published, the authors do not sufficiently identify the isomer used, presumably using (-)-HCA (Soni et al., 2004).

Bioavailability

The bioavailability of HCA-SX was evaluated by Loe et al. (2001) in four healthy adult volunteers. These authors administered 2 g of HCA-SX under fasting conditions and measured plasma concentrations of HCA-SX every 30 minutes for a total period of four hours. HCA-SX plasma concentrations were 0.8 μg/mL 30 minutes after administration and 8.4 μg/mL two hours after intake. The maximum post-administration peak ranged from 4.7 to 8.4 μg/mL. Although plasma levels of HCA-SX began to decrease at 2.5 hours after ingestion, these remained substantially higher than pre-administration values. This study shows that after an acute intake of HCA-SX absorption is relatively fast, and the product remains available in plasma for several hours.

Possible Action Mechanisms

HCA was identified by Watson and Lowenstein (1970) as a potent competitive inhibitor of the extramitochondrial enzyme adenosine triphosphate-citrate (pro-3S)-lyase, which is involved in the extramitochondrial synthesis of fatty acids. Through this mechanism, it has been observed both in vitro and in vivo experiments that HCA induces a reduction of Acetil-CoA, thus limiting the biosynthesis of fatty acids and cholesterol in a variety of tissues (Lowenstein, 1971; Sullivan, 1974). In a double-blind, placebo-controlled randomized cross-over study performed on ten sedentary lean male subjects, Kovacs and Westerterp-Plantenga (2006) examined whether the HCA may reduce de novo lipogenesis after 7-day high-carbohydrate, a low-fat diet with ingestion of HCA, or a placebo. The authors reported an increase of net fat synthesis as de novo lipogenesis, calculated as the difference between fat balance and fat intake, which tended to be lower in subjects treated with HCA than in those in the placebo group, although differences between the two groups were not statistically significant. Furthermore, it has been proposed that the inhibitory effect of HCA on glycolysis increases rates of hepatic glycogen synthesis. Thus, glycogen influences glucoreceptors in the liver inducing satiation via the vagus nerve (Sullivan et al., 1974; 1984), contributing to the suppression of food intake and decreasing body weight gain. In this regard, several studies have shown that HCA can improve the release and availability of serotonin, a neurotransmitter involved in the control of appetite. Ohia et al., (2001; 2002) evaluated the in vitro acute effects of the administration of 1 mM HCA on the cerebral cortex of rats. These results showed increases in serotonin release and availability. Subsequently, clinical trials conducted by Preuss et al., (2004; 2004) reported the same results in humans.

Other authors have attempted to explain the action of HCA on body-weight regulation through the ability and efficiency of this acid in the modulation of genes involved in the lipid and carbohydrate metabolism and cell communication (Roy et al., 2004). Treatment of human adipocytes with HCA-SX resulted in a significant down-regulation of 348 and induction of 366 fat- and obesity-related genes such as hormone sensitive lipase, Peroxisome Proliferator-Activated Receptors gamma (PPARγ) coactivator 1α, leptin, and Hypoxia-Inducible Factor-1 genes. Taken together, these results support the antilipolytic and antiadipogenic role of HCA-SX (Roy et al., 2007). More recently, it has been suggested that the effect of HCA intake on body weight regulation might be partially explained through its regulation of leptin and insulin plasma levels. It has been reported that in mice treated with an extract of *G. cambogia* for four weeks, plasma insulin and leptin levels tended to be lower than those of the control mice, and the decrease in insulin was found to be statistically significant (Hayamizu et al., 2003).

ANIMAL TOXICITY STUDIES

The aim of this section is to provide the information currently available on the evaluation of the safety of using HCA in animals. Different studies have been published evaluating short and long-term acute toxicity effects of HCA. Several studies have also been conducted to analyze the specific effects of direct skin

and eye exposure to HCA. Finally, research has also been carried out on genotoxicity and reproduction. These studies have been conducted in different animal species, mainly rats and rabbits.

In a previous review, Soni et al., (2004) analyzed various safety issues related to the use of HCA. In this paper, the studies reviewed by Soni and coworkers are re-evaluated, in addition to others that have not been discussed or published since 2003.

Short and Long-Term Effects

Ohia et al., (2002) evaluated the acute effects of the use of HCA-SX for 14 days. They studied Albino rats (5 females and 5 males) fed ad libitum and receiving a dose of 5000 mg/kg through a gastric probe. They evaluated mortality, clinical signs, and weight or anatomic and histopathological changes of the craniocerebral, chest, and abdominal systems through a necropsy performed at the end of the intervention period. The authors did not report any deaths or significant clinical changes except on day three of HCA-SX administration, when a rat was found to have a pustule on the back of its head. No significant weight changes or tissue injuries were observed during the necropsy. The authors, therefore, concluded that the administration of HCA-SX was not associated with any acute adverse events. Thus, the LD50 of HCA-SX administered orally to rats was estimated to be over 5000 mg/kg weight.

Several studies of variable time length (from 4 to 30 days) and doses administered (150 mg to 1500 mg) have been conducted by different authors, although none of them assessed HCA intake toxicity as their primary objective. Of the studies analyzed, none of them have mentioned possible adverse events recorded after HCA intake during treatment (Leonhardt et al., 2001; 2004; Rao and Sakariah, 1988). Furthermore, no adverse effects were found in animal studies comparing different chemical forms or preparations (Regulator®, Citrin K®, Super Citrimax®) containing HCA (Louter-van de Haar et al., 2005).

Leonhardt and Langhans (2002) analyzed the effects of the oral administration of HCA on food intake and the recovery of weight loss in 23 rats. After a period of ten days of energy restriction and weight loss, rats were fed ad libitum for 22 days with diets containing 1% or 12% of weight as total fat and supplemented with 3% HCA (1500 mg/kg). Rats in the HCA group showed a significantly lower body weight regain compared to the control group. However, long-term suppression of food intake was only observed in rats fed the 12% fat diet with a significant reduction in the number of meals, not in meal size. But because treatment with HCA did not affect plasma levels of β-hydroxybutyrate in rats, this study does not support the hypothesis that food intake suppression might be mediated by an increase in hepatic fatty acid oxidation. No adverse effects on animals were reported during HCA administration.

Several clinical trials with similar characteristics, in terms of dose and time of exposure to HCA but using other experimental animals, showed similar results. Chee et al., (1977) did in vitro and in vivo research into the influence of HCA on the synthesis of fatty acids in chicken and rat livers, and in rat adipose tissue. Although in vitro they observed a reduction in the synthesis of fatty acids in the animal (though there were differences between the two animal species), in vivo they failed to demonstrate this inhibition of the synthesis with a diet containing 52.6 nmols/kg of HCA. With regard to the in vivo study, the authors reported an increase in the peripheral levels of triglycerides, which was not found in rats. They did not report undesirable effects to the animals during the study.

Some studies have shown toxicological effects of HCA in animals when administered for over 30 days, although the results are extremely contradictory. Shara et al., (2003; 2004) analyzed the effects of HCA intake on weight, testicular and liver lipid peroxidation, and DNA fragmentation, in addition to possible histopathological changes in seven Sprague-Dawley rats. The animals received 0, 0.2, 2, and 5% HCA (0–2500 mg/kg) in their diet. The rats were killed at 30, 60, and 90 days of treatment. At 90 days of HCA administration the investigators found weight loss in the rats studied, with no changes in liver or testicular lipid peroxidation or in DNA fragmentation. No hematological or biochemical disorders (hemoglobin, hematocrit, albumin, lymphocytes, cholesterol, glucose, calcium, phosphorus, potassium, sodium, and iron) or significant histopathological changes were seen in the different vital organs studied (brain, heart, kidneys, liver, prostate, spleen, and testes), attributable to the use of HCA. Also, no mortality differences were seen among the different animal groups treated. However, Saito et al., (2005) researched the ability of HCA to inhibit body fat deposition in obese Zucker rats (5 groups of 6 rats) and the safety of taking high amounts of HCA. The animals received supplements for 92 or 93 days with different doses of HCA (0, 10, 51, 102, and 154 mmol/kg of feed). The authors did not see changes in total body weight. However, the intake of high doses of HCA (154 mmol/kg of feed) resulted in an inhibition of fat storage in the epididymus. Furthermore, it was shown that diets with a high HCA content ($\geq$102 mmol/kg of feed, equivalent to 778–1244 mg/kg body weight) were associated with testicular atrophy and toxicity, while low-HCA diets ($\leq$51 mmol/kg of feed, equivalent to $\leq$389 mg/kg of body weight/day) were shown to be safe. Discrepancies between the two studies could be related to the lactone content of HCA affecting its solubility. The lower levels of testicular testosterone production associated with obese male Zucker rats in comparison to lean rats, and the effect of dietary imbalances that may have contributed to the observed testicular toxicity which, as Burdock et al., (2005) have pointed out, was not clearly described in the Saito study (2005). However, Saito and coworkers suggest that doses 10- to 16- times greater than those recommended as dietary supplements do not cause testicular atrophy.

Various long-term studies conducted in experimental animals ($>$4 weeks) have also found that HCA favorably affects glucose metabolism, blood pressure, lipid peroxidation, and bodyweight (Hayamizu et al., 2003; Talpur et al., 2003; Roy et al., (2004). The variability in the results obtained seems to depend particularly on the chemical form of HCA used. However, none

of the studies mentioned have described an increase in animal mortality, or other toxicological changes induced by HCA.

Effects on the Skin

Some studies suggest that HCA applied directly to the skin may cause acute skin injuries; however, the chronic oral use of HCA has not shown effects to the skin either in studies carried out in humans or those performed in experimental animals.

Ohia et al., (2002) studied the acute effects (24 hours of exposure) of the administration of a dose of 2000 mg/kg of HCA on the skin of Albino rabbits (5 females and 5 males). They evaluated mortality, emergent clinical signs, body weight changes, and histopathological changes in the craniocerebral, chest, and abdominal systems after a necropsy performed at the end of the study period. The authors did not report any deaths during the study under the experimental conditions. Between days 0 and 2 of the intervention only one rabbit had mucoid feces, without any other clinical findings. All rabbits had slight erythema on the skin but none of them had edema. Desquamation was noted on eight sites out of ten animals after seven days of exposure. During the autopsy, skin reddening was seen at the site of exposure in two animals, and pale kidneys were found in one animal. There were no other significant histopathological changes in any of the examined tissues at the terminal necropsy. Oikawa et al., (2005) also studied the effect of HCA on different skin properties (collagen and triglyceride content, thickness of skin, collagen layers, and subcutaneous tissue). These authors observed that animals receiving diets supplemented with 3.3% HCA show a decrease in the total number of adipocytes with no adverse effects on the skin properties tested.

Effects on Erythropoiesis

Recently Oluyemi et al., (2007) assessed the erythropoietic effect of a *G. cambogia* extract in rats. Twenty-one adult male rats were randomized into three dosage groups of *G. cambogia* (0, 200, and 400 mg/kg) for five weeks. The study reported a significant increase in red blood cell count and a decrease in animal weight in the treated groups. The increase in hematocrite found by the authors might be partly explained by high *G. cambogia* iron content and the presence of antioxidants, which preserve the average life span of red blood cells. Also, the flavonoid component of *G. cambogia* is known to increase the level of peripheral testosterone, which may stimulate erythropoiesis in humans.

Effects on the Eyes

Few clinical trials have investigated the potential toxicological effects of HCA on the eyes. However, Ohia et al., (2002) evaluated it in a safety study, so it is worth mentioning. These researchers administered 54 mg of HCA into the conjunctiva of the right eye of six Albino rabbits, while the left eye was used as control. Acute ocular reactions were examined after 1, 24, 48, and 72 hours and at 4, 7, 14, and 21 days of exposure. After seven days they reported discharge and inflammation in the conjunctiva of half of the rabbits, as well as an increase in the presence of small blood vessels. In two of the three affected rabbits, the injuries persisted until day 21 of exposure. Inflammation that did not affect the cornea was also seen in the eye. The results suggest that in some animals HCA can induce inflammatory reactions both in the iris and the conjunctiva.

This study indicates that the direct application of HCA into the eye may cause eye irritation. However, whether the oral administration of HCA could cause undesirable effects on this organ has not yet been studied, but it is unlikely as nobody has reported it in the studies performed in animals or humans.

Genotoxicity

The mutagenic properties of HCA were studied (Aujoulat, 2003) in an in vitro bacterial mutagenicity test. Five strains of *Salmonella typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) were used to evaluate the effects of HCA on the presence and absence of metabolic activation. Different doses of exposure to HCA were used (52, 164, 512, 1600, and 5000 μg/plaque). Using an in vitro bacterial mutagenicity test, the authors concluded that HCA has no mutagenic effects either with or without metabolic activation (Soni et al., 2004).

Similarly to the previous study, in vitro bacterial genotoxicity studies carried out with citric acid or its sodium and tripotassium salts did not show mutagenic effects either (EPA, 2001).

Reproductive Studies

During the fetal development period there is a high demand on lipid production for growth. The lipids produced by the mother are transferred through the placenta to the fetus for tissue synthesis. HCA inhibits the synthesis and storage of lipids and therefore may be critical for gestational development. This hypothesis was tested by Jones and Ashton (1976) through a study conducted in pigs in which they concluded that neither the synthesis nor the fetal storage of lipids is affected by HCA intake. Likewise, in rat fetuses, Xu et al., (1990) found that the synthesis of fatty acids is not affected by HCA intake. Some authors suggest that lipid synthesis in fetuses and adult rats may differ, which would explain the lack of HCA action observed in the synthesis of fatty acids in the fetus (Watson and Lowenstein, 1970; Lowenstein, 1971; Jones and Ashton, 1976).

Calorie restriction (20–35% total intake) and body weight loss (>20%) were associated with a reduction of fertility and reproduction in rats (Fan et al., 1997; Wu et al., 2002; Terry et al., 2005). Because HCA intake has been associated with the control of body weight it would be interesting to study the

effects of HCA intake on animal reproduction. Unfortunately, we have not found any studies that test this hypothesis.

EVALUATION IN HUMANS

Materials and Methods

Data for this review were obtained by searching Medline or PubMed and the ISI Web of Science with the key words: "*Garcinia cambogia in humans*," "body weight loss and *Garcinia cambogia*," "*Garcinia cambogia* and body weight," "*Garcinia cambogia* and body fat," "*Garcinia cambogia* and cholesterol," "*Garcinia cambogia* and triglycerides," "*Garcinia cambogia* and lipids," "*Garcinia cambogia* and adverse effects," "*Garcinia cambogia* and safety," "Hydroxycitric acid," and "*Garcinia cambogia* and blood."

The criteria for selecting the studies were the following. They had to be a) randomized, clinical trials, controlled with placebo, b) carried out in humans, c) published in a scientific journal in the database of Science Citation Index or Medline between January, 1990 and January, 2010, d) original, and e) they must have evaluated changes in weight, body composition, plasma lipid profile, adverse clinical, or biochemical effects.

We finally selected 16 randomized placebo-controlled studies. Once the articles had been selected, the following significant data were extracted: author and year, number of participants (randomized/completed trial), type of individuals studied (normoweight, overweight, or obese), length of intervention, *G. cambogia* extract or HCA dose administered (mg/day), use of other antiobesity substances associated with the intervention, control of food intake and physical activity, placebo used, changes in weight and/or blood lipid profile, changes in satiety, and undesirable clinical or biochemical effects.

Efficacy in Body Weight and Composition

After extensively reviewing the literature, we found 15 studies (see Table 1) that appeared in peer-review literature and that evaluated the effect of *G. cambogia* extracts on human body weight. These are eleven randomized, double-blind, placebo-controlled, parallel studies involving 738 subjects (Conte, 1993; Ramos et al., 1995; Girola et al., 1996; Heymfield et al., 1998; Antonio et al., 1999; Thom 2000; Mattes and Bormann, 2000; Preuss et al., 2005; Opala et al., 2006; Toromanyan et al., 2007, Vasques et al., 2008), one randomized, single-blind, placebo-controlled, parallel clinical trial (Hayamizu et al., 2001), two chronic cross-over studies (Kovacs et al., 2001; Westerterp-Plantega and Kovacs, 2002), one randomized single-blind acute study (Gatta et al., 2009), and one re-examination (Preuss et al., 2005) of the data from two previous randomized, double-blind, placebo-controlled, parallel studies (Preuss 2004; 2004). Studies published in the form of abstracts have been excluded from this review (Thom 1996; Rothacker and Watman, 1997; Kaats et al., 1998; Preuss et al., 2002). The largest study with the higher number of subjects ($n = 144$) was that of Girola et al., (1996). However, the duration of the experiment in this study was only a period of four weeks. The study showed that groups treated with one or two capsules of a product containing *G. cambogia* extract, *chitosan*, and chromium decreased their body weight by 7.9% and 12.5%, respectively, versus a 4.3% reduction in the placebo group ($p < 0.001$).

Several authors have used *G. cambogia* extracts alone (Ramos et al., 1995; Heymfield et al., 1998; Mattes and Borman, 2000; Hayamizu et al., 2001; Opala et al., 2006; Gatta et al., 2009) or in conjunction with other potential antiobesity components (Conte 1993; Girola et al., 1996; Antonio et al., 1999; Thom, 2000; Kovacs et al., 2001; Preuss et al., 2005; Toromanyan et al., 2007; Vasques et al., 2008), and the study administered it with tomato juice (Westerterp-Plantega and Kovacs, 2002), which has made it difficult to determine the isolated effect of *G. cambogia.* Preuss et al., (2004; 2004) analyzed the effect of supplementation using optimal doses of a highly bioavailable form of hydroxycitric acid (HCA-SX) alone, in combination with niacin-bound chromium and with a standardized *Gymnema sylvestre* extract. The authors found significant body weight loss in the groups treated with *G. cambogia*, but the changes were not significantly higher than those found in the placebo group. However, after combining their data with data from two previous studies (Preuss et al., 2004; 2004) they observed statistically significant differences in weight loss between groups, confirming that HCA-SX plus niacin bound chromium and *Gymnema sylvestre* extract can reduce body weight and BMI more effectively than a placebo (Preuss et al., 2005).

In most of the published studies, both the treated and the placebo groups received lifestyle recommendations, except in two studies where the subjects were asked to maintain their regular diet and level of physical activity (Toromanyan et al., 2007; Vasques et al., 2008). Many times, low-calorie diets were used (associated or not with physical exercise or low fat content) (Conte 1993; Ramos et al., 1995; Girola et al., 1996; Thom, 2000; Mattes and Bormann et al., 2000) or a high fiber content (Heymfield et al., 1998). In some cases a normocaloric diet was prescribed during the intervention (Antonio et al., 1999), or a diet ad libitum (Westerterp-Plantega and Kovacs, 2002; Toromanyan et al., 2007; Gatta et al., 2009).

It is important to note that most of the studies analyzed7break; ($n = 9$) were conducted with small sample sizes ($\leq$60 subjects) and frequently on overweight or obese subjects. In most of the studies we reviewed the groups receiving *G. cambogia* extract (associated or not with other possible active ingredients) tended to have a greater weight loss compared to the control group or placebo group. However, in only six studies (Ramos et al., 1995; Girola et al., 1996; Thom, 2000; Mattes and Bormann, 2000; Preuss et al., 2005; Toromanyan et al., 2007) was weight loss found to be significantly higher in the intervention group compared to the control group.

Table 1 Summary of *Garcinia cambogia* published studies in humans

		SUBJECTS						EFFECT ON			UNDESIRABLE EFFECTS	
REFERENCE	DESIGN	Number	Type	INTERVENTION	OTHERS ANTIOBESITY SUBTANCIES USED	DURATION	LIFESTYLE CONDITIONS	WEIGHT	LIPID PROFILE	SATIETY	CLINICAL	BIOCHEMICAL
Conte (1993)	Parallel, randomized, double-blind, placebo-controlled	54/39*	Overweight and obese	1500 mg GCE + 300 μg chromium picolinate /day	Chromium picolinate	8 wk	Low fat diet and physical exercise	No significant differences between groups	Not determined	Not determined	Itching around the mouth (without significant difference between groups)	Not determined
Ramos et al., (1995)	Parallel, randomized, double-blind, placebo-controlled	40/35	Obese	1500 mg GCE/day	NO	8 wk	Low-calorie, low-fat diet	Higher significant weight loss in the GCG vs. placebo ($p < 0.05$)	Higher significant reduction in TC and TG vs. placebo ($p < 0.05$)	Not determined	Headache and nausea (without significant difference between groups)	No
Girola et al., (1996)	Parallel, randomized, double-blind, placebo-controlled	150/144	Overweight and obese	1 o 2 capsules/day of 55 mg GCE + 19 mg chromium + 240 mg *chitosan*/day	*Chitosan*	4 wk	Low-calorie diet	Higher significant weight loss in the GCG vs. placebo ($p < 0.001$)	Higher significant dose-dependent reduction of TC LDL-c and increase of HDL-c	Not determined	Nausea and headache (without significant difference between groups)	No
Heymfield et al., (1998)	Parallel, randomized, double-blind, placebo-controlled	135/84	Overweight	3000 mg GCE/day	NO	12 wk	Low calorie and high-fiber diet.	No significant differences between groups	Not determined	Not determined	Intestinal disorders, headache, or upper airway symptoms (without significant difference between groups)	Not determined
Antonio et al., (1999)	Parallel, randomized, double-blind, placebo-controlled	20/18	Overweight and obese	750 mg GCE, 750 mg calcium, 750 mg *guggulsterone* extract, 750 mg L-tyrosine/day	*Guggulsterone and* L-tyrosine	6 wk	Normocaloric diet and exercise program	No significant differences between groups	Not determined	Not determined	No reported adverse effects	No
Thom (2000)	Parallel, randomized, double-blind, placebo-controlled	40/33	Obese	300 mg CGE + 1200 mg *Phaseolus vulgaris* + 1200 mg inulin/day	*Phaseolus vulgaris* and inulin	12 wk	Low-calorie diet	Higher significant weight loss in the GCG vs. placebo	Not determined	Not determined	No reported adverse effects	No
Mattes & Bormann (2000)	Parallel, randomized, double-blind, placebo-controlled	167/89	Overweight	2400 mg GCE /day	NO	12 wk	Low-calorie diet	Higher significant weight loss in the GCG vs. placebo ($p < 0.05$)	Not determined	No differences between groups	No reported adverse effects	Not determined
Kovacs et al., (2001)	Cross-over, randomized, double-blind, placebo-controlled	21/21	Normal weight to moderately obese	500 mg HCA (alone) or with 300 medium-chain TG/day	Medium-chain TG	3 periods of 2 wk	3 isoenergetic snacks	No significant differences between treatments	Not determined	No differences between treatments	No reported adverse effects	Not determined

Hayamizu et al., (2001)	Parallel, randomized, single-blind, placebo-controlled	40/40	Overweight and obese	1000 mg HCA/day	NO	8 wk	Not specified	No significant effects on weight between groups. Higher significant reduction of visceral fat n the GCG vs. placebo ($p < 0.01$)	No significant differences between groups	Not determined	No reported adverse effects	No
Westerterp-Plantega and Kovacs (2002)	Cross-over randomized, single-blind, placebo-controlled	24/24	Overweight	Juice of tomato enriched with 900 mg HCA/day	NO	2 periods of 2 wk	No calorie restriction	No significant differences between groups	Not determined	Higher significant reduction in energy intake in GCG vs. placebo ($p < 0.005$)	No reported adverse effects	Not determined
Preuss et al., (2005)	Parallel, randomized, double-blind, placebo-controlled	90/82	Overweight and obese	2800 mg HCA alone or with 4 mg niacin-bound chromium and 400 mg *Gymnema* silvestra extract	Chromium *Gymnema* silvestra extract	8 wk	2000 kcal diet. Supervised physical exercise	Higher significant weight reduction in the GCG alone or combined ($p < 0.001$)	Significant reduction LDL, triglycerides and higher HDL in the GCG combination	Higher significant reduction in energy intake in GCG alone or combined vs. placebo	No reported adverse effects	Increased metabolites of fat oxidation
Opala et al., (2006)	Parallel, randomized, double-blind, placebo-controlled	105/98	Overweight and obese	GCE plus extracts of kidney bean pods, and chromium yeast (content non specified)	NO	12 wk	Low-calorie diet and exercise program	No significant differences on weight between groups. Higher significant body fat loss in the GCG vs. placebo ($p < 0.01$).	No significant differences between groups	Not determined	No reported adverse effects. More gastrointestinal symptoms in GCG vs. placebo	No
Toromanyan et al., (2007)	Parallel, randomized, double-blind, placebo-controlled	80/58	Obese	396 mg GCE/day	*Matricaria chamomilla*, *Rosa damascene*, *Lavandula officinalis* and *Cananga odorata*	8.6 wk	Habitual diet and physical activity	Higher significant weight loss in the GCG vs. placebo ($p < 0.001$)	No significant differences between groups	Not determined	Not determined	Not determined
Vasques et al., (2008)	Parallell, randomized, double-blind study	82/58	Obese	2400 mg GCE plus 1500 mg *Amorphophallus konjac* extract/day	*Amorphophallus konjac*	12 wk	Habitual diet and physical activity	No significant differences between groups	Significant reduction in TC and LDL-c leves in GCE vs control groups	Not determined	No significant differences in adverse events between groups	NO
Hayamizu et al., (2008)	Parallel, randomized, double-blind, placebo-controlled	44/44	Normal or overweight and obese	1000 mg GCE/day	NO	12 wk	Not specified	Not determined	Serum TG non-significantly decreased in GCE group	Not determined		No effects on serum testosterone, estrone or estradiol levels
Gatta et al., (2009)	Parallel, randomized, single blind cross-over acute study	12/8	Normal weight	320 mg Etomoxir 2000 mg HCA and placebo	NO	1 day separated by 1 wk	Breakfast and lunch ad libitum	Not determined	Not determined	HCA significantly increased satiety but not energy intake in a subsequent meal	Not determined	Plasma NEFA concentrations were higher and β-hidroxybutyrate lower after HCA and Etomoxir than placebo.

Abbreviations: GCE: *Garcinia Cambogia* Extract; GCG: *Garcinia Cambogia* Group; HCA: Hidroxycytric acid; wk: weeks; TC: total cholesterol; TG: triglycerides; LDL-c: low-density lipoprotein-cholesterol; HDL-c: high-density lipoprotein- cholesterol. NEFA: Non-esterified fatty acids.

*Randomized/completed trial.

Several authors have described higher fat loss in subjects treated with *G. cambogia* extracts compared to those who were not treated, without significant differences in body weight (Hayamizu et al., 2001; Opala et al., 2006). Likewise, a randomized, double-blind clinical trial revealed significant decreases in body fat in overweight subjects who had received the dietary supplement over a 12-week period in comparison with a placebo group (Opala et al., 2006). However, the results of the Heymfield et al., (1998) study show that treatment with *G. cambogia* did not produce significant weight and fat mass loss beyond that observed with a placebo.

Although several studies in humans have shown a significant effect on body weight or fat associated with the intake of *G. cambogia* extracts, none of them have examined whether these effects persist beyond the 12 weeks of intervention.

Several of the studies reviewed here have also evaluated the effect of the administration of *G. cambogia* on appetite and satiety, and some of them have shown a significant favorable effect on the treated group with regard to these variables (Westerterp-Plantega and Kovacs, 2002; Preuss et al., 2005; Gatta et al., 2009).

Effect on Lipid Profile

A total of 8 of the 16 studies revised have investigated the effects of the administration of a *G. cambogia* supplement on lipid profiles. Ramos et al., (1995) in a randomized, placebo-controlled clinical trial conducted on 40 obese patients, showed a significant reduction in total cholesterol and triglyceride concentrations in the group treated with 1.5 g of *G. cambogia* extract. Likewise, Girola et al., (1996) analyzed the effect on the lipid profile of a formula containing *G. cambogia* administered to 150 obese subjects for four weeks. These subjects were randomized to take 0, 1, or 2 capsules of a mixture containing 240 mg of *chitosan*, 55 mg of an extract of *G. cambogia*, and 19 mg of chromium per day. The authors found a statistically significant higher reduction in low-density lipoprotein cholesterol and triglyceride concentrations, and a significant increase of high-density lipoprotein levels in the group treated with two capsules per day. Preuss et al., (2005) reported that after eight weeks groups treated with HCA-SX alone or HCA-SX combined with niacin-bound chromium and standardized *Gymnema sylvestre* extracts showed significant decreases in low density lipoprotein and triglycerides levels, while the levels of high-density lipoprotein were found to have increased more than in the placebo group. The remaining studies in our review did not measure lipid profiles, and the majority reported no significant differences between groups, although a tendency for higher cholesterol levels and lower triglyceride levels was reported in the *G. Cambogia* treated group in three of them (Hayamizu et al., 2001; Opala et al., 2006; Toromanyan et al., 2007). Recently, in a double-blind randomized 12 week trial, 32 subjects were assigned to a treatment group (2.4 g of *G. Cambogia* plus 1.5 g of Konjac) and 26 subjects to a placebo group. The results of the study show significant reductions in total cholesterol and low-density lipoprotein cholesterol, but no significant effect on triglycerides levels in the *G. Cambogia* group compared to the placebo group (Vasques et al., 2008)

Adverse Events in Human Studies

In this section we analyze the adverse events reported in the literature on clinical trials carried out in human subjects after the administration of *G. cambogia* extract.

A total of 13 studies were found in the literature that analyzed the mid-term effects of the administration of HCA isolated from *G. cambogia.* These studies included a total of 930 subjects. In all but five of them (Girola et al., 1996; Antonio et al., 1999; Thom. 2000; Kovaks and Westerterp-Plantenga, 2001), the amount of Garcinia extract used in the studies ranged between 1500 and 4667 mg/day (25–78 mg/kg body weigh/day). The equivalent dose of HCA ranged between 900 and 2800 mg/day (15–47 mg/kg body weight/day). In these clinical trials it was possible to analyze both tolerance to the supplement and the safety of taking it, though in the majority of cases that was not the specific objective of the study. Hayamizu and coworkers (2008) specifically investigated the possible adverse effects relating particularly to reproductive toxicity after *G. Cambogia* supplementation in humans. The authors concluded that the intake of a *G. Cambogia* extract at dose levels commonly recommended for humans does not affect serum sex hormone levels and routine blood parameters. Recently, there has been controversy regarding the hepatotoxicity of the Hydroxycut dietary supplement. On the basis of one case series, Lobb (2009) hypothesized that the putative hepatotoxicity of this supplement may be due to its HCA component. Conversely, other authors claim that there is no sufficient evidence to demonstrate that such hepatotoxicity is associated with HCA consumption (Stohs et al., 2009). Additional studies should be conducted in the future to demonstrate this possible adverse effect and to determine its cause.

Table 1 summarizes the adverse events and the tolerability found in each of these studies. None of them reported serious adverse events attributable to the intake of *G. cambogia* extracts. In most of the studies no adverse events were seen or reported with the administration compounds containing HCA. The studies relevant to safety or tolerability issues are described below.

In a randomized, placebo-controlled study, Ramos et al., (1995) studied the effects of the administration of a lyophilized *G. cambogia* extract in overweight patients. The subjects were randomized to receive an extract of *G. cambogia* (500 mg capsules) or placebo before each main meal for eight weeks. The authors observed headache and nausea in two of the patients in the treated group and one in the placebo group. The authors did not report significant changes in various biochemical parameters, including serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), or blood glucose.

In the study conducted by Girola et al., (1996), the incidence of adverse events (nausea or headache) in the two groups treated with *G. cambogia* extract was not higher than the incidence seen in the placebo group. Moreover, no significant changes

attributable to supplements containing the active ingredient were found in hematological or biochemical parameters.

In 1998, Heymsfield et al., used a randomized, placebo-controlled parallel design to evaluate the efficacy of the administration of a *G. cambogia* extract (50% HCA) on body composition. One hundred and thirty-five overweight patients were randomized to receive 1.5 g of HCA or a placebo, in both cases in conjunction with a low-calorie, high-fiber diet. Forty-two patients in the active treatment group and 42 patients in the placebo group completed the study. A total of 19 patients reported gastrointestinal symptoms (6 from the control group vs. 13 from the treated group), 21 reported headaches (12 vs. 9, respectively), and 29 reported effects to their upper airways (13 vs. 16, respectively) although the differences between groups did not reach statistical significance. The authors did not study changes in biochemical parameters or the full blood count between groups.

Hayamizu et al., (2001), in a randomized, placebo-controlled study, investigated the effect of HCA on body composition in 40 overweight or obese patients. The subjects were randomized to receive 1 g of HCA or placebo for a period of eight weeks. The treated group experienced a higher reduction ($p < 0.01$) in visceral fat area measured by computerized axial tomography than the placebo group. The authors did not observe adverse events that could be attributed to the use of the active supplement. Several hematological (white blood cells, granulocytes, hemoglobin, hematocrit, and blood platelets) and biochemical parameters (SGOT, SGPT, γ-glutamil transpeptidase, lactate dehydrogenase, blood ureic nitrogen, creatinine, glucose, insulinemia, and ketone bodies) were also measured at weeks 4 and 8 of the study. A significant reduction in hemoglobin levels was observed in both groups, and was therefore not attributable to the treatment.

Finally, the human studies conducted by Preuss et al., (2004; 2004; 2005) did not report serious adverse events in any of the subjects and no subjects were removed or dropped out of the study due to adverse events. But in one study, several adverse incidents such as leg cramps, heartburn, diarrhea, gas, increased appetite, headaches, stomach burn, and menstrual disorders were observed. However, the number of patients reporting light adverse events was not significantly different

CONCLUSIONS

Although there have been several studies reporting the effects of supplements containing *G. cambogia* extracts on body weight in both experimental animals and humans, we should be cautious when interpreting these results as there have been other randomized, placebo-controlled clinical trials that have not had the same outcome. Most studies in humans have been conducted on small samples and mainly in the short term. There is still little evidence to support the potential effectiveness and long-term benefits of *G. cambogia*.

With regard to toxicity or safety, it is important to note that *G. cambogia* has traditionally been used in human diet or as a supplement (as a therapeutic preparation) for centuries, without reports of adverse effects from its use. Except in rare cases, studies conducted in experimental animals have not reported increased mortality or significant toxicity. And no differences were found in humans in terms of side effects or adverse events (those studied) between groups treated with *G. cambogia* and the placebo groups at the doses used. Further research into animal reproduction and particularly into long-term efficacy and safety in humans would be appropriate.

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