



## Hydroxycitric acid does not promote inflammation or liver toxicity

Dallas L Clouatre, Harry G Preuss

Dallas L Clouatre, Glykon Technologies Group, LLC, Seattle, WA 98109, United States

Harry G Preuss, Department of Physiology, Georgetown University Medical Center, Washington, DC 20057, United States

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Correspondence to: Dallas L Clouatre, PhD, Glykon Technologies Group, LLC, 24 Roy Street No. 401, Seattle, WA 98109, United States. [dallasclouatre@mac.com](mailto:dallasclouatre@mac.com)

Telephone: +1-510-2894331 Fax: +1-206-9253568

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### Abstract

Garcinia cambogia extract (GC) with its active component consisting of hydroxycitric acid (HCA) is widely utilized for weight loss. Various HCA salts are available, including calcium, magnesium, potassium and mixtures of these. Experimentally, these salts exhibit different properties with some, but not all, improving glucose tolerance and blood pressure. Recently, obesity-prone C57BL/6J mice were fed a high-fat diet (HFD, 45 kcal% fat) with or without GC (1%, w/w) for 16 wk. The active arm reduced visceral fat, adipocyte size and serum glucose, yet purportedly also exhibited hepatic collagen accumulation, lipid peroxidation and increased mRNA levels of genes related to oxidative stress. The latter findings are at odds with a large body of animal and human studies that have been conducted on the safety and efficacy of HCA. This literature shows HCA to be protective against the liver toxicity associated with ethanol and dexamethasone administration, and to maintain serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase at near normal levels. In both animal and clinical literature, elevated intakes of HCA *per se* have not led to signs of inflammation or hepatotoxicity. The compound has

been found to reduce markers of inflammation in brain, intestines, kidney and serum.

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**Key words:** *Garcinia cambogia*; Hepatic collagen; Hepatic inflammation; Hepatic oxidative stress; Hydroxycitric acid; Metabolic syndrome; Tumor necrosis factor- $\alpha$ ; Weight loss

**Core tip:** The preponderance of animal and human studies of *Garcinia cambogia* extract have found it to reduce markers of inflammation in brain, intestines, kidney and serum and to be either protective or neutral in terms of liver health. The limited reports of toxicities thus far have been linked to improperly manufactured materials and/or to peculiarities with the animal models used. The available data indicate that *Garcinia cambogia* extract/hydroxycitric acid does not cause liver toxicity.

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### TO THE EDITOR

Kim *et al*<sup>[1]</sup> recently reported that a *Garcinia cambogia* extract (GC, 1%, w/w) fed to C57BL/6J mice in conjunction with a high-fat diet (HFD, 45 kcal% fat) for 16 wk protected against “HFD-induced obesity by modulating adipose fatty acid synthesis and  $\beta$ -oxidation but induces hepatic fibrosis, inflammation and oxidative stress<sup>[1]</sup>.” A review of this article in light of other published research on (-)-hydroxycitric acid (HCA), the active component in GC, raises a number of questions. The most significant

are these: what was the form of HCA used (not indicated) and is the toxicity reported induced by HCA *per se* or, instead, was it caused by the source of HCA/GC tested? These issues are particularly acute inasmuch as the results of Kim *et al.*<sup>11</sup> are at variance with numerous published studies involving both animals and humans, several of which indicate that HCA actually exerts a protective effect upon the liver.

Differences among various sources of HCA can be quite significant, yet against copious evidence, it too often is assumed that all sources of HCA are the same in terms of physiology. In the study in question, the tested compound is not fully identified. The only information provided is that the tested compound provided “1%, w/w, 60% hydroxyl citric acid” and was provided by Newtree Inc. of the United States (although Newtree appears to be a South Korean company). Whether this material was stabilized with calcium, potassium, sodium, *etc.* or some mixture of these is not revealed. Similarly, no information is provided on the free acid or lactone content, whether the extraction process is novel or established, the amount of residual toxins, such as chloride ion, left in the extract, and so forth and so on. For instance, some HCA calcium salts contain up to approximately six percent halogenated compounds due to improper processing of starting materials that had been dried with the help of sodium chloride—is the material used by Kim *et al.*<sup>11</sup> one of these?

That the nature of the HCA-containing source is important was made clear years ago in a critical analysis of another study that purported to demonstrate toxicity, in that particular case, testicular toxicity, at high dosages. This was a study by Saito *et al.*<sup>21</sup>. When examined closely by Burdock *et al.*<sup>22</sup>, it was determined that the HCA salt tested was very unusual in that it contained a high lactone content and that the weight loss results were not typical of literature on HCA. In this case, the particular animal model also turned out to have been inappropriately chosen. Hence, in an instance of supposed testicular toxicity, there were unacceptable levels of uncertainty about the compound being tested. Moreover, various aspects of the study design and its assumptions proved to be questionable.

Kim *et al.*<sup>11</sup> remind the reader of the “potential for hepatotoxicity of hydroxycut, a formulation that contains GC among other ingredients<sup>11</sup>.” Not mentioned is the fact that after almost two decades of free sale of HCA products, there appear to be no reports of human liver toxicity aside from those involving Hydroxycut and only 8 out of 14 of the Hydroxycut formulas associated with liver toxicity even contained HCA/GC! The safety, including liver safety, of HCA as relates to Hydroxycut and other products was evaluated at length by Stohs *et al.*<sup>41</sup> and no evidence of toxicity was found. In retrospect, the common denominator in these cases appears to be green tea extracts. Animal models have established the hepatotoxicity of high oral doses of (-)-epigallocatechin-3-gallate<sup>51</sup>. Reviews of human usage strongly suggest a causal association, albeit an idiosyncratic one, between green tea consumption and liver damage<sup>61</sup>. In contrast, quite a number of reviews

have affirmed that HCA is extremely safe. These include Chuah *et al.*<sup>71</sup>, Márquez *et al.*<sup>81</sup> and Stohs *et al.*<sup>91</sup>.

Published studies involving both animal models and humans indicate that HCA *per se* is either neutral with regard to the liver or actively protective. For instance, GC in a rat model has been tested against toxic challenge to the liver by both ethanol and dexamethasone. Mahendran and Devi<sup>101</sup> demonstrated that GC supplementation was sufficient to prevent undesirable changes in the lipid profile on dexamethasone administration and also to protect normal liver phospholipid levels. Likewise, when rats were challenged with ethanol to induce peroxidation damage to the liver, Devi and Mahendran<sup>111</sup> found “co-treatment of the rats with *Garcinia cambogia* significantly inhibited the rise in lipid levels and also the peroxidative damage caused by ethanol, which is evident from the improved antioxidant status. The levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase were maintained at near normalcy in *Garcinia cambogia* treated rats”. Similar protection was provided by GC with regard to liver superoxide dismutase, catalase and various glutathione compounds.

The study of Clouatre and Preuss, which lasted eight weeks and involved high-fat/high-sugar diets in rats, found results that are in line with those of Mahendran and Devi<sup>110-121</sup>. In healthy and relatively young animals, HCA treatment compared with control led to strong trends towards reduced CRP and tumor necrosis factor- $\alpha$  without exerting significant effects on ALT and AST. These results are similar to those found in a formal safety assessment of a commercial potassium-calcium hydroxycitrate salt (60% HCA) by Soni *et al.*<sup>131</sup>, which was designed, in part, specifically to look for potential hepatotoxicity. The gavage administration of this salt at doses up to 2500 mg/kg per day for a period of 90 d did not lead to any significant adverse effects, including in the histological examinations of the livers of the test and control arms. Given the high dosage of HCA and the time frame comparable to that of Kim *et al.*<sup>11</sup>, the results of the study by Soni *et al.*<sup>131</sup> in the rat rodent model clearly are at variance with the findings in the mouse model and in line with other research reports of HCA's safety. The human equivalent dosage of HCA in the Soni study is approximately 30 g in a 60 kg individual.

There have been at least four published studies of the safety of HCA in humans and these trials reached the same conclusion confirming the safety of the oral consumption of HCA salts. The studies are those of Hayamizu *et al.*<sup>141</sup>, Hayamizu *et al.*<sup>151</sup>, Ishii *et al.*<sup>161</sup> and Hayamizu *et al.*<sup>171</sup>. None of these studies found any significant adverse effects on the liver. Hayamizu *et al.*<sup>141</sup> in a study lasting three months, but involving only 1000 mg HCA per day (*i.e.*, 1666 mg of a 60% salt) found no significant change in any liver parameter. Hayamizu *et al.*<sup>161</sup> found no observed adverse effects 4000 mg HCA per day for ten days and Hayamizu *et al.*<sup>171</sup> found no adverse effects at 3000 mg HCA for 30 d.

Finally, the issue of GC and inflammation needs to be

addressed more generally. Clouatre *et al*<sup>[18]</sup> were the first researchers to discover that HCA consumption relieves a number of markers of inflammation and this information was confirmed in Clouatre *et al*<sup>[12]</sup>. A number of recent studies now have established these findings regarding HCA and inflammation. A study using rats performed by dos Reis *et al*<sup>[19]</sup> found that the “antiinflammatory effects provided by the *Garcinia cambogia* extract result in an improvement of several parameters analysed (sic) in experimental colitis and could provide a source for the search for new antiinflammatory compounds useful in inflammatory bowel disease treatment.” Similar protective effects have been found by Amin *et al*<sup>[20]</sup> in relation to a high fat diet, metabolic disturbances and brain oxidative dysfunction and by Amin *et al*<sup>[21]</sup> in relation to renal oxidative stress on a high fat and high sucrose diet.

## REFERENCES

- 1 **Kim YJ**, Choi MS, Park YB, Kim SR, Lee MK, Jung UJ. *Garcinia Cambogia* attenuates diet-induced adiposity but exacerbates hepatic collagen accumulation and inflammation. *World J Gastroenterol* 2013; **19**: 4689-4701 [PMID: 23922466]
- 2 **Saito M**, Ueno M, Ogino S, Kubo K, Nagata J, Takeuchi M. High dose of *Garcinia cambogia* is effective in suppressing fat accumulation in developing male Zucker obese rats, but highly toxic to the testis. *Food Chem Toxicol* 2005; **43**: 411-419 [PMID: 15680676]
- 3 **Burdock G**, Soni M, Bagchi M, Bagchi D. *Garcinia cambogia* toxicity is misleading. *Food Chem Toxicol* 2005; **43**: 1683-1684; author reply 1685-1686 [PMID: 15993998]
- 4 **Stohs SJ**, Preuss HG, Ohia SE, Kaats GR, Keen CL, Williams LD, Burdock GA. No evidence demonstrating hepatotoxicity associated with hydroxycitric acid. *World J Gastroenterol* 2009; **15**: 4087-4089 [PMID: 19705510]
- 5 **Lambert JD**, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (-)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol* 2010; **48**: 409-416 [PMID: 19883714]
- 6 **Mazzanti G**, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, Mastrangelo S. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009; **65**: 331-341 [PMID: 19198822]
- 7 **Chuah LO**, Yeap SK, Ho WY, Beh BK, Alitheen NB. In vitro and in vivo toxicity of garcinia or hydroxycitric Acid: a review. *Evid Based Complement Alternat Med* 2012; **2012**: 197920 [PMID: 22924054]
- 8 **Márquez F**, Babio N, Bulló M, Salas-Salvadó J. Evaluation of the safety and efficacy of hydroxycitric acid or *Garcinia cambogia* extracts in humans. *Crit Rev Food Sci Nutr* 2012; **52**: 585-594 [PMID: 22530711]
- 9 **Stohs SJ**, Lau FC, Kim D, Kim SU, Bagchi M, Bagchi D. Safety assessment of a calcium-potassium salt of (-)-hydroxycitric acid. *Toxicol Mech Methods* 2010; **20**: 515-525 [PMID: 20946014]
- 10 **Mahendran P**, Devi CS. Effect of *Garcinia cambogia* extract on lipids and lipoprotein composition in dexamethasone administered rats. *Indian J Physiol Pharmacol* 2001; **45**: 345-350 [PMID: 11881574]
- 11 **Mahendran P**, Devi CS. The Modulating Effect of *Garcinia Cambogia* Extract on Ethanol Induced Peroxidative Damage in Rats. *Indian J Pharmacol* 2001; **33**: 87-91
- 12 **Clouatre D**, Preus HG. Potassium Magnesium Hydroxycitrate at Physiologic Levels Influences Various Metabolic Parameters and Inflammation in Rats. *Current Topics in Nutritional Research* 2008; **6**: 201-210
- 13 **Soni MG**, Burdock GA, Preuss HG, Stohs SJ, Ohia SE, Bagchi D. Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt. *Food Chem Toxicol* 2004; **42**: 1513-1529 [PMID: 15234082]
- 14 **Hayamizu K**, Tomi H, Kaneko I, Shen M, Soni MG, Yoshino G. Effects of *Garcinia cambogia* extract on serum sex hormones in overweight subjects. *Fitoterapia* 2008; **79**: 255-261 [PMID: 18316163]
- 15 **Hayamizu K**, Ishii Y, Kaneko I, Shigematsu N, Okuhara Y, Tomi H, Furuse M, Yoshino G, Shimasaki H. Safety of *Garcinia cambogia* Extract in Healthy Men- High-Doses Administration Study I. *J Oleo Sci* 2003; **52**: 499-504 [DOI: 10.5650/jos.52.499]
- 16 **Ishii Y**, Kaneko I, Shen M, Hayamizu K, Shigematsu N, Tomi H, Yoshino G, Shimasaki H. Safety of *Garcinia cambogia* Extract in Healthy Volunteers- High-Dose Administration Study II. *J Oleo Sci* 2003; **52**: 663-671 [DOI: 10.5650/jos.52.663]
- 17 **Hayamizu K**, Ishii Y, Kaneko I, Shigematsu N, Okuhara Y, Hiroyuki Sakaguchi H, Shigematsu N, Shimasaki H. No-Observed-Adverse-Effect Level (NOAEL) and Sequential-High-Doses Administration Study on *Garcinia cambogia* Extract in Humans. *J Oleo Sci* 2002; **51**: 365-369 [DOI: 10.5650/jos.51.365]
- 18 **Clouatre D**, Talpur N, Talpur F, Echard B, Preuss H. Comparing metabolic and inflammatory parameters among rats consuming different forms of hydroxycitrate. *J Am Coll Nutr* 2005; **24**: 429
- 19 **dos Reis SB**, de Oliveira CC, Acedo SC, Miranda DD, Ribeiro ML, Pedrazzoli J, Gambero A. Attenuation of colitis injury in rats using *Garcinia cambogia* extract. *Phytother Res* 2009; **23**: 324-329 [PMID: 18979524]
- 20 **Amin KA**, Kamel HH, Abd Eltawab MA. The relation of high fat diet, metabolic disturbances and brain oxidative dysfunction: modulation by hydroxy citric acid. *Lipids Health Dis* 2011; **10**: 74 [PMID: 21569551]
- 21 **Amin KA**, Kamel HH, Abd Eltawab MA. Protective effect of *Garcinia* against renal oxidative stress and biomarkers induced by high fat and sucrose diet. *Lipids Health Dis* 2011; **10**: 6 [PMID: 21235803]

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