Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.4087

World J Gastroenterol 2009 August 28; 15(32): 4087-4089
World Journal of Gastroenterology ISSN 1007-9327

No evidence demonstrating hepatotoxicity associated with hydroxycitric acid

Sidney J Stohs, Harry G Preuss, Sunny E Ohia, Gilbert R Kaats, Carl L Keen, Lonnie D Williams, George A Burdock

Sidney J Stohs, Harry G Preuss, Sunny E Ohia, Gilbert R Kaats, Carl L Keen, Lonnie D Williams, George A Burdock, School of Pharmacy and Health Professions, Creighton University Medical Center, 4967 Stillwater Trail, Frisco, TX 75034, United States
Author contributions: Stohs SJ, Preuss HG and Ohia SE developed the primary draft; Kaats GR, Keen CL, Williams LD and Burdock GA made the major additions and editing.
Correspondence to: Dr. Sidney J Stohs, Dean Emeritus, School of Pharmacy and Health Professions, Creighton University Medical Center, 4967 Stillwater Trail, Frisco, TX 75034, United States. sstohs@yahoo.com
Telephone: +1-214-2156655 Fax: +1-972-3349474
Received: July 6, 2009 Revised: July 17, 2009
Accepted: July 24, 2009
Published online: August 28, 2009

Abstract

Although a number of cases of hepatotoxicity are associated with the use of Hydroxycut weight management products, it has been alleged that their effects are primarily due to the presence of hydroxycitric acid (HCA, as Super CitriMax) in the formulations. However, while these products contain up to 20 different ingredients, some do not contain HCA. Case studies reported to date have not considered in depth the literature on the numerous animal and human studies that have been conducted on the safety and efficacy of HCA. No HCA-associated hepatotoxicity or treatment-related adverse effects have been reported in these studies, and thus it is premature to make the assumptions presented in the recent case studies regarding Hydroxycut. If it is established in well controlled studies that the use of these formulations with and/or without HCA can result in the occurrence or progression of hepatotoxicity, additional studies should be conducted to characterize the causative factor(s).

Key words: Hydroxycitric acid; Super CitriMax; Hydroxycitric acid-SX; Garcinia cambogia; Hydroxycut; Liver failure; Hepatotoxicity; Safety and efficacy

Peer reviewer: Xiao-Ming Yin, MD, PhD, Associate Professor of Pathology, Associate Director, Division of Molecular Diagnostics, Department of Pathology, University of Pittsburgh School of Medicine, Scaife Hall, 7th Fl, Room S739, 3550 Terrace Street, Pittsburgh, PA 15261, United States

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(32): 4087-4089 Available from: URL: http://www.wjgnet.com/1007-9327/15/4087.asp DOI: http://dx.doi.org/10.3748/wjg.15.4087

TO THE EDITOR

In the Letter to the Editor by Lobb[1], the author has hypothesized that the putative hepatotoxicity of the dietary supplement, Hydroxycut, may be due to one of its components, namely hydroxycitric acid (HCA)derived from *Garcinia cambogia*. However, it is important to note that, of the 14 different formulations of Hydroxycut that have been marketed, only 8 contain HCA. In general, these products are cocktails containing up to 20 different ingredients. In the case studies cited by the author[1], information is not provided regarding the specific Hydroxycut products that were used in each of the case reports. This is of concern given that of the numerous ingredients present in these products, no specific reason was given for identifying HCA as the putative hepatotoxic agent other than as the possible hepatotoxic agent in some of the previous case reports. Because of the name of this product line, it is understandable that a possible word association might be made with HCA. Can the reported hepatotoxicity of these products (assuming it is correct) be attributed to an ingredient or combination of ingredients? No information or discussion was presented regarding the potential hepatotoxicity of any of the other ingredients or combinations of ingredients, and it is distracting to make inferences without sound research support.

The importance of the issues raised above is underscored by the numerous animal[2-8] and human[5,9-12] studies on the safety and efficacy of HCA (as Super CitriMax, HCA-SX). Regrettably, none of these studies was referenced and discussed by the author of this Letter to the Editor[1]. In experimental animal studies at up to 25X the human equivalency dose of HCA, no reports are available on hepatotoxicity or other adverse effects. A HCA dose of 2500 mg/kg, equivalent to 150 000 mg in a 60 kg individual, had no adverse effect in the tested animals[2-4].

Soni *et al*[5] have summarized the results of 15 HCA human clinical studies, 14 of them were double blind and placebo controlled, and one was a single arm, open trial. No treatment-related adverse effects have been reported in any of these studies. These authors concluded that HCA at a level up to 2800 mg/d is safe for human consumption. The combined data strongly suggest that HCA itself is not the culprit with respect to the case studies reporting hepatotoxicity associated with Hydroxycut use. In the Health Hazard Report on Hydroxycut by Mozersky *et al*[13], the Board noted that it did not know what ingredient(s) present in these products can cause hepatotoxicity, assuming the products are indeed the causative agents. More studies are needed before a definitive conclusion can be made.

Interestingly, several animal studies have suggested that HCA may have hepatoprotective[14,15] and chemoprotective[16] properties. In addition, Kaats[17] has recently conducted a 60-d study on 25 human subjects using a product containing 4600 mg/d of HCA. The results showed no evidence of adverse effects and indicated hepatoprotection based on decreasing values for the hepatic enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

It should be noted that the dried fruit of *Garcinia cambogia*, a source of HCA, has been consumed for centuries throughout Southeast Asia[18] and is in the USDA' s list of Perennial Edible Fruits[19]. Consistent with the above findings, HCA (as Super CitriMax) has been generally recognized as safe (GRAS) by the Burdock Group, one of the nation's leading food ingredient safety and toxicology groups.

Finally, a key issue that was not discussed by Lobb[1] is the possibility that other co-consumed substances, such as acetaminophen, alcohol, or a wide range of prescription drugs, may have been responsible for the hepatotoxicity. The referenced case study by Shim and Saab[20] does in fact note that acetaminophen was consumed along with aspirin. Acetaminophen toxicity is the leading cause for calls to Poison Control Centers in the United States and results in almost 500 deaths annually due to acute liver failure[21].

There is no question that issues exist with respect to the regulation, quality control, and appropriate safety and efficacy studies of supplements, just as there are issues with numerous drugs, including acetaminophen, that cause extensive morbidity and mortality.

However, to point an accusatory finger at an ingredient that has been extensively studied and for which no adverse effects have been reported in animal and human studies, is counterproductive.

Given the widespread use of dietary supplements in the USA as well as in other countries, it is imperative that sound science should be used in the evaluation of the potential negative as well as the positive effects of these products. With respect to the potential negative effects of some of these products, an important step forward in this regard is the current requirement for adverse event reporting. However, it is important to note that these reports typically reflect the associations, rather than the clear-cut cases of causality. When the associations are noted, they should be rigorously examined, and if the supplements are found to be the causative factors for the pathology reported, the true agents need to be firmly identified, along with the dose at which the negative effects are induced.

REFERENCES

1 **Lobb A**. Hepatoxicity associated with weight-loss supplements: a case for better post-marketing surveillance. *World J Gastroenterol* 2009; **15**: 1786-1787

2 **Ohia SE**, Opere CA, LeDay AM, Bagchi M, Bagchi D, Stohs SJ. Safety and mechanism of appetite suppression by a novel hydroxycitric acid extract (HCA-SX). *Mol Cell Biochem* 2002; **238**: 89-103

3 **Shara M**, Ohia SE, Yasmin T, Zardetto-Smith A, Kincaid A, Bagchi M, Chatterjee A, Bagchi D, Stohs SJ. Dose- and time-dependent effects of a novel (-)-hydroxycitric acid extract on body weight, hepatic and testicular lipid peroxidation, DNA fragmentation and histopathological data over a period of 90 days. *Mol Cell Biochem* 2003; **254**: 339-346

4 **Shara M**, Ohia SE, Schmidt RE, Yasmin T, Zardetto-Smith A, Kincaid A, Bagchi M, Chatterjee A, Bagchi D, Stohs SJ. Physico-chemical properties of a novel (-)-hydroxycitric acid extract and its effect on body weight, selected organ weights, hepatic lipid peroxidation and DNA fragmentation, hematology and clinical chemistry, and histopathological changes over a period of 90 days. *Mol Cell Biochem* 2004; **260**: 171-186

5 **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

6 **Deshmukh NS**, Bagchi M, Yasmin T, Bagchi D. Safety of a novel calcium/potassium salt of hydroxycitric acid (HCA-SX): I. Two-generation reproduction toxicity study. *Toxicol Mech Meth* 2008; **18**: 433-442

7 **Deshmukh NS**, Bagchi M, Yasmin T, Bagchi D. Safety of a novel calcium/potassium salt of (-)-hydroxycitric acid(HCA-SX): II. Developmental toxicity in rats. *Toxicol Mech Meth* 2008, **18**: 443-451

8 **Roy S**, Rink C, Khanna S, Phillips C, Bagchi D, Bagchi M, Sen CK. Body weight and abdominal fat gene expression profile in response to a novel hydroxycitric acid-based dietary supplement. *Gene Expr* 2004; **11**: 251-262

9 **Preuss HG**, Bagchi D, Bagchi M, Rao SCV, Satyanarayana S, Dey DK. Effect of a novel, natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin-bound chromium and Gymnema sylvestre extract in weight management in human volunteers. *Nutr Res* 2004; **24**: 45-58

10 **Preuss HG**, Rao SCV, Garis RI, Bramble JD, Ohia SE, Bagchi M, Bagchi D. An overview of the safety and efficacy of a novel, natural (-)-hydroxycitric acid extract (HCA-SX) for weight management. *J Med* 2004; **33**: 33-48

11 **Preuss HG**, Bagchi D, Bagchi M, Rao SCV, Dey DK, Satyanarayana S. Effects of a natural extract of (-)hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and Gymnema sylvestre extract on weight loss. *Diab Obes Metab* 2004; **6**: 171-180

12 **Preuss HG**, Garis RI, Bramble JD, Bagchi D, Bagchi M, Rao SCV, Satyanarayana S. Efficacy of a novel calcium/potassium salt of (-)-hydroxycitric acid in weight control. *Int J Clin Pharm Res* 2005; **XXV**: 133-144

13 **Mozersky DO**, Klonz K, Katz LM. The Problem: Liver toxicity following consumption of dietary supplement, Hydroxycut. Health Hazard Review Board FDA 2009. http://www.fda.gov/oc/opacom/hottopics/hydroxycut/

HHE.pdf
14 **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
15 **Mahendran P**, Sabitha KE, Devi CS. Prevention of HCl-ethanol induced gastric mucosal injury in rats by Garcinia cambogia extract and its possible mechanism of action. *Indian J Exp Biol* 2002; **40**: 58-62
16 **Mahendran P**, Vanisree AJ, Shyamala Devi CS. The antiulcer activity of Garcinia cambogia extract against indomethacin-induced gastric ulcer in rats. *Phytother Res* 2002; **16**: 80-83
17 **Kaats GR**. Safety and Efficacy of a (-)hydroxycitric acid containing product in human subjects. (personal communication)
18 Anon. CSFII 1994-1996(2000), Agricultural Research Service, U.S. Department of Agriculture, Washington, DC
19 Anon. Perennial Edible Fruits of the Tropics, An Inventory, U. S. Department of Agriculture Handbook No. 642, 1987
20 **Shim M**, Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. *Dig Dis Sci* 2009; **54**: 406-408
21 **Lee WM**. Acetaminophen and the U.S. Acute Liver Failure Study Group: lowering the risks of hepatic failure. *Hepatology* 2004; **40**: 6-9

S- Editor Li LF **L- Editor** Wang XL **E- Editor** Ma WH