Safety and Efficacy of *Hydroxycitric Acid* Derived from *Garcinia cambogia* – A Literature Review

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Introduction

A number of cases of hepatotoxicity have been associated with the use of Hydroxycut®, a line of weight management products produced by Iovate Health Sciences, Inc. (Mississouga, Ontario, Canada),[1-5] which resulted in the removal of these products from the market in May of 2009.[6] A majority of these case studies[3-5] alleged that the hepatotoxic effects may be primarily due to the presence of hydroxycitric acid (HCA, as the proprietary ingredient Super CitriMax®, InterHealth, Benicia, CA, derived from the fruit rinds of *Garcinia cambogia*) in the formulations. However, these products contain up to 20 different ingredients, and 8 of the 14 marketed Hydroxycut products did not contain HCA. No information was provided regarding the names of the specific Hydroxycut products used in the individual case reports,[1-6] although in 2 cases the product was identified as "Newly formulated Hydroxycut" and the 12 ingredients were listed (one of which was HCA).[1] The focus on HCA appears to be due solely to the word association between the chemical term "hydroxycitric acid" and "Hydroxycut," as noted by an author of one the case reports.[5] Because of this word association, it may be inappropriately assumed that all Hydroxycut products contain HCA.

The case studies[1-5] did not consider or discuss in-depth the relevant literature on the numerous human, animal, and *in vitro* studies that have been conducted on the safety and efficacy of HCA. No significant HCA-associated hepatotoxicity or treatment-related adverse effects have been reported in the variously controlled studies that have been conducted on HCA, and thus the present safety review concludes that it is inappropriate to make the assumptions regarding HCA that have been presented in the recent case studies involving Hydroxycut.

Background

HCA is a popular ingredient used in weight loss and weight management supplements. It is a natural extract derived from the dried fruit rind of *Garcinia cambogia* (Clusiaceae), a tree native to Southeast Asia and India, commonly known as the Malabar tamarind.[7] The dried fruit rind contains about 16–26% HCA[8,9] and is used extensively for culinary purposes in Asian countries, where it has been consumed for centuries without harmful effects. It possesses a distinct sweet and sour taste, which it imparts to foods, and when added to foods has been reported to make them more filling and satisfying.[7,10] The form of HCA widely used in weight management products is a calcium/potassium salt of 60% HCA (known as Super CitriMax),[11-13] although products containing 50% HCA as the calcium salt are also used. The first studies involving the effects of HCA on lipid metabolism were conducted in the 1970s.[14-16]

Garcinia cambogia. Photo ©2010 Steven Foster

Safety Studies

Various animal[11-13,17-21] and human[22-27] studies have been conducted on the safety of HCA. In summary, no serious or significant untoward effects were reported in any of those studies. All reported effects were comparable to placebo-treated animals and human subjects. Dose-dependent studies in animals by Ohia et al. assessed acute oral toxicity, as well as acute dermal toxicity, primary dermal irritation, and primary eye irritation.[11] No gross toxicological findings were observed, and the authors concluded that HCA is safe under the experimental conditions employed. In subchronic (90 day) toxicity studies in rats treated with various doses of HCA, Shara et al. did not observe any significant changes in organ histopathology, hepatic or testicular lipid peroxidation, or DNA fragmentation.[12]

At right: Illustration of *Garcinia cambogia* by Roques, Joseph. *Phytographie Médicale ... Paris: Chez l'Auteur,* de l'Imprimerie de Didot le Jeune, 1821. (Vol. 2, plate 140). Courtesy of Hunt Institute for Botanical Documentation, Carnegie Mellon University, Pittsburgh, PA.


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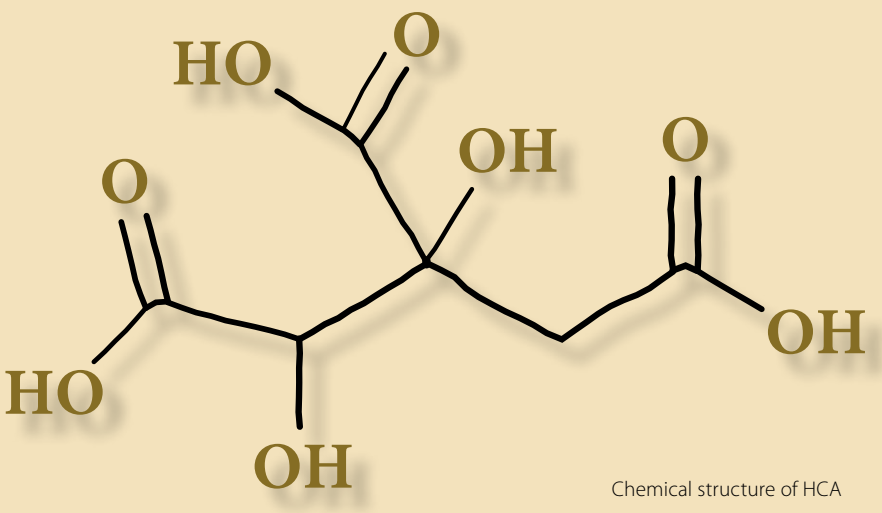
Furthermore, HCA produced no changes in hematology or clinical chemistry as compared to control animals.[13]

The safety of the potassium/calcium salt of HCA was assessed in 2-generation reproductive toxicity[19] and developmental toxicity[20] studies in male and female rats. The feeding of up to 10,000 ppm (parts per million) HCA in the diet did not affect reproductive performance in either sex based on fertility and mating, sexual maturity, gestation, parturition, litter size, or offspring development. Furthermore, no evidence of maternal toxicity or evidence of fetal soft tissue, skeletal, or external abnormalities were noted. HCA was not teratogenic at these experimental conditions.

In another study, the effect of HCA on insulin resistance, oxidative stress, and inflammation was assessed in male Zucker rats over a period of 7 weeks.[21] Compared to control animals, malondialdehyde, protein carbonyl formation, and protein tyrosine nitration (markers of oxidative stress) were significantly lower in the kidney and liver of rats given HCA. Levels of C-reactive protein and interleukin-6 (markers of inflammation) were lower in plasma as compared to control animals. Furthermore, fasting plasma insulin, glucose, and triglycerides, as well as body weights and food intake, were lower in HCA-treated animals as compared to controls. Insulin resistance did not develop in HCA-supplemented animals but did develop in the controls.[21]

In experimental animal studies at up to 25 times the human equivalency dose of HCA, there have been no reports of hepatotoxicity or other adverse effects. An HCA dose of 2500 mg/kg, equivalent to 150,000 mg in a 60 kg individual, was without adverse effects, including hepatotoxicity or testicular toxicity, in the test animals.[11-13] In a single study involving suppression of fat accumulation in male Zucker obese rats, HCA doses of 778 mg/kg and 1244 mg/kg were reported to cause testicular atrophy.[28] These doses greatly exceed the 35-40 mg HCA/kg dose that is recommended and widely used for weight management in humans,[22-26] and these results are not supported by other animal studies, including 2-generation animal reproduction studies.[11-13,17-21]



Chemical structure of HCA

An excellent summary of the results of 15 HCA human clinical studies has been provided by Soni et al.[26] and Downs et al.[27] Of these studies, 14 of them were double-blind and placebo-controlled, and one was a single-arm, open trial. Over 750 total subjects were involved in these studies. No significant adverse effects were reported in any of these studies following treatment with HCA. No pathologic or clinically significant changes in hematologic assays or blood chemistries, including liver enzymes, were observed. These authors concluded that HCA at levels up to 2800 mg/day were safe for human consumption. A more recent study has shown that HCA administered to overweight subjects for 12 weeks did not significantly alter serum testosterone, estrone, or estradiol levels.[29] This study also affirmed that administration of HCA did not reveal any adverse effects with respect to hematology and serum clinical pathology parameters.

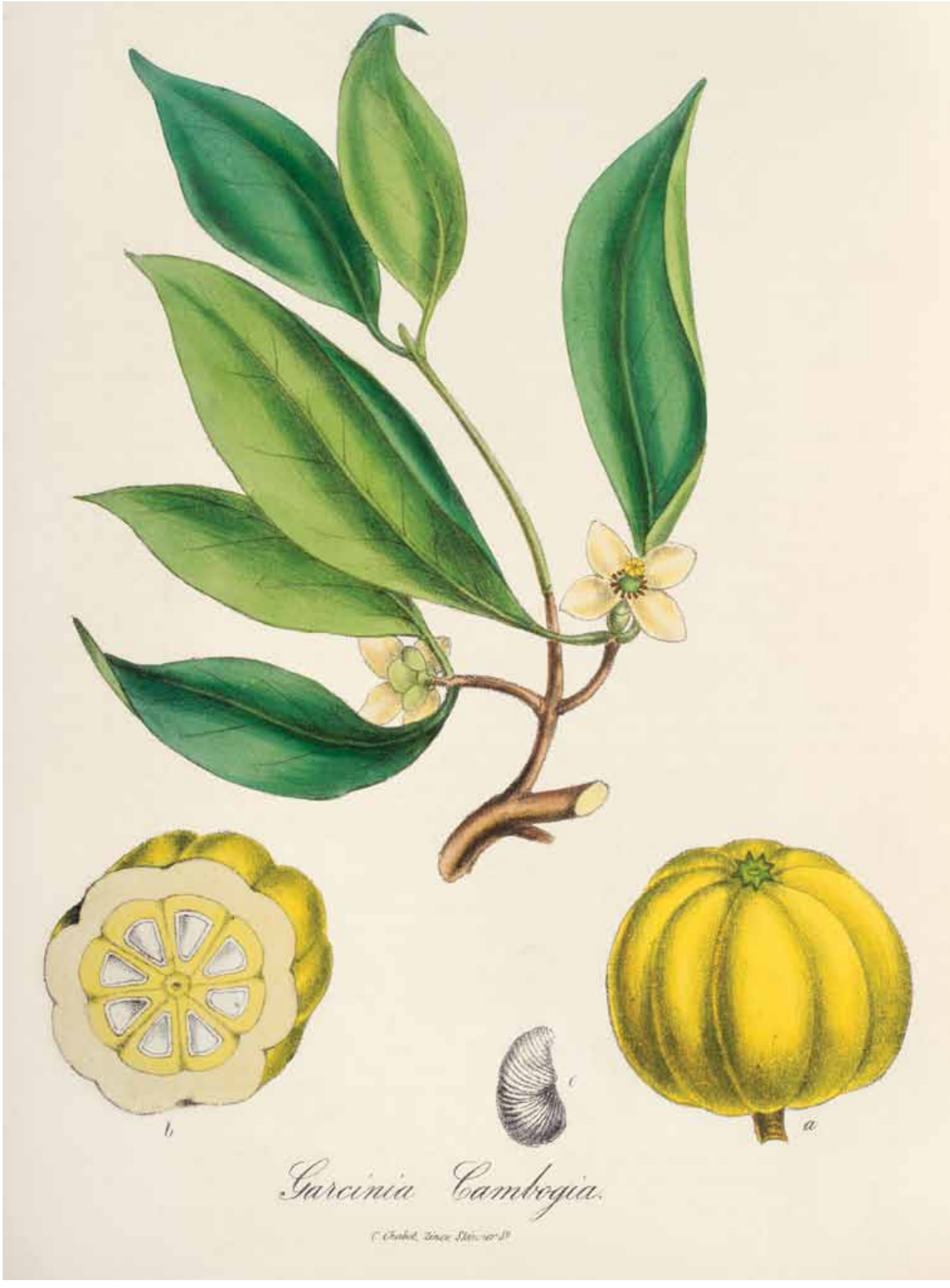
The combined human and animal data suggest that HCA in and of itself is not the culprit with respect to hepatotoxicity in the case studies associated with the use of Hydroxycut products. However, it should be kept in mind that HCA in combination with other ingredients in the Hydroxycut products might rarely be responsible, or that the incidence of HCA-induced hepatotoxicity is so rare that it has not been detected to date in animal studies and human clinical trials.

In the US Food and Drug Administration (FDA) Health Hazard Report on Hydroxycut by Mozersky et al., the Board noted that it was unclear what ingredient(s) present in these products were responsible for inducing hepatotoxicity, assuming the products were indeed the causative agents.[6] It should be noted that in the FDA Report, a total of 23 cases of Hydroxycut-associated liver toxicity, including those in the 5 published case study reports,[1-5] were identified over the past 8 years through the Center for Food Safety and Applied Nutrition's adverse event monitoring system. The possibility exists that other co-consumed substances as acetaminophen, alcohol, anabolic steroids, or a wide range of prescription drugs, as well as various hepatic pathogens, sub-clinical hepatic steatosis, or a combination of the above, may have been responsible for the hepatotoxicity reported in these cases. Furthermore, contaminants in the products may have been potentially responsible.

It is of interest that several animal studies have suggested that HCA may exert properties against HCl-ethanol, dexamethasone, and indomethacin-induced tissue damage.[30-32] One of the authors of this article (G.R. Kaats) has completed a 60-day study on 25 human subjects using a product containing 4600 mg HCA/day. The unpublished results showed no evidence of adverse effects and suggested hepatoprotection based on decreasing values for the hepatic enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Furthermore, for several individuals with modestly elevated enzyme levels, upon receiving HCA these enzymes returned to within the normal range. In addition, in an *in vitro* protein glycation (glycosylation) system, Bousova et al. demonstrated that HCA decreased the formation of glycation products, again suggesting a protective role for HCA.[33] Glycation is a process associated with the pathogenesis of diabetic complications, as well as aging.

As previously noted, the dried fruit and rind of *Garcinia cambogia*, the source of HCA, have been consumed for centuries throughout Southeast Asia.[7,10] In addition to eating the fruit, the rind is mashed and used to make a broth or soup to which other ingredients such as vegetables or rice are added. Furthermore, *G. cambogia* is in the US Department of Agriculture's (USDA) list

At right: Illustration of *Garcinia cambogia* by Burnett, M.A. *Plantae Utiliores, or Illustrations of Useful Plants, Employed in the Arts and Medicine.* London: Whittaker & Co., 1842-1850. (Vol. 1, plate 16b)
Courtesy of Hunt Institute for Botanical Documentation, Carnegie Mellon University, Pittsburgh, PA.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of Perennial Edible Fruits.[34] Consistent with the above, HCA (as Super CitriMax) has been identified to be generally recognized as safe (GRAS) by the Burdock Group, one of the nation's leading food ingredient safety and toxicology groups. These authors noted that over the past 10 years, approximately 5 billion doses of HCA (as Super CitriMax) have been sold and consumed as a dietary supplement with no reports of significant adverse, reproductive, or teratogenic effects.[26] Mild gastric upset is the most common, but infrequent, complaint.

Efficacy Studies

The ability of orally-administered HCA to promote weight loss and contain body weight gain in experimental animals has been demonstrated in various studies,[11-21] beginning as early as 1971.[14] Most of these studies have been conducted in rat species. The effectiveness of HCA was dependent upon dose, the form of HCA used, the duration of treatment, the animal species, and the general experimental design. The common observation throughout these diverse studies is that HCA administration results in weight loss and/or retards body weight gain (with no significant adverse effects).

As stated previously, in-depth reviews of the efficacy of HCA in weight loss and weight management involving human clinical trials have been published by Soni et al.[26] and Downs et al.[27] Eleven studies assessed the effects of HCA on weight loss, with 7 studies demonstrating a statistically significant effect while 2 studies showed a trend toward significance. Several explanations were given for lack of a positive effect in some studies,[35,36] including low dose of HCA, short duration of the study, poor patient compliance, and low bioavailability of the form (calcium salt only) of HCA used. Many of the studies measured only weight loss and not the relationship between fat loss and muscle gain as emphasized by Preuss et al.[24] Several studies that did not assess weight loss demonstrated increased fat oxidation[37,38,39] and a decreased accumulation of visceral fat.[29] Again, none of these studies demonstrated significant adverse effects.

It is imperative that sound science be used in the evaluation of the potential positive as well as negative effects of herbal ingredients and dietary supplements, given the worldwide use of these products.

Several mechanisms of action have been shown to be involved with respect to the weight loss/weight management effects of HCA. The ability of HCA to act as a competitive inhibitor of the enzyme ATP-citrate lyase may be the primary mechanism.[26-28] This enzyme catalyzes the conversion of citrate and coenzyme A to acetyl coenzyme A (acetyl Co-A) and oxaloacetate. Acetyl Co-A is a critical building block in the biosynthesis of fatty acids, cholesterol, and lipids, as well as the neurotransmitter acetylcholine. Thus, the primary mechanism of HCA is believed to involve the inhibition of fat synthesis.[39]

Several other mechanisms may also be involved. For example, Ohia et al. have shown that HCA inhibits serotonin uptake in isolated rat brain cortical slices in a manner similar to selective serotonin reuptake inhibitors (SSRIs),[11] and this action may therefore constitute the mechanism whereby HCA suppresses appetite.[23] Roy et al., using a GeneChip repeated high-density microarray, determined the effects of HCA on body weight and abdominal fat gene expression in rats.[40] HCA supplementation selectively influenced approximately 1% of 9960 genes in fat tissue without affecting genes responsible for transcribing mitochondrial and nuclear proteins. Furthermore, HCA was shown to up-regulate genes encoding serotonin receptors, thus providing a mechanistic basis for the actions of HCA at the genetic level.

Summary and Conclusions

An ever increasing number of well-designed and appropriately controlled studies in animals and humans have indicated that HCA is both safe and efficacious. Safety studies in experimental animals at up to 25 times the human equivalency doses did not produce hepatotoxicity or other significant adverse effects. Furthermore, a number of *in vivo* and *in vitro* studies have indicated that HCA may be hepatoprotective and chemoprotective.

There is no question that issues exist with respect to the appropriate safety and efficacy of herbal ingredients and dietary supplements, as well as their regulation and quality control—just as there are issues with numerous government-approved conventional drugs, including over-the-counter drugs such as acetaminophen, which cause extensive morbidity and mortality. However, to point an accusatory finger at an ingredient that has been extensively studied and for which no significant adverse effects have been reported in animal and human studies at commonly used doses is not only unreasonable, but scientifically indefensible and even counterproductive. If it were to be established in well-controlled animal studies that the use of specific Hydroxycut formulations can result in the induction of hepatotoxicity, additional studies should be conducted to characterize the causative factor(s). No such trials are known to be in progress, and human clinical studies certainly cannot be conducted to establish the hepatotoxicity of specific Hydroxycut products.

It is imperative that sound science be used in the evaluation of the potential positive as well as negative effects of herbal ingredients and dietary supplements, given the worldwide use of these products. The recently-enacted legal requirement for reporting of serious adverse events is an important step forward in assessing and monitoring potential negative effects of dietary supplements, and the good manufacturing practices (GMPs) being implemented by the FDA with respect to dietary supplements should prove beneficial in preventing untoward effects from contaminants, adulterants, or inappropriate amounts of known ingredients. In addition to these new industrial regulatory safeguards, efficacy and safety studies will continue to be important means for objectively evaluating dietary supplement ingredients and products. HG

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References

1. Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with the use of the herbal weight-loss supplement Hydroxycut [letter]. *Ann Intern Med.* 2005;142:477–478.
2. Jones FJ, Andrews AH. Acute liver injury associated with the herbal supplement Hydroxycut in a soldier deployed in Iraq. *Am J Gastroenterol.* 2007;102:2357.
3. Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: A case series and review of liver toxicity from herbal weight loss supplements. *World J. Gastroenterol.* 2008;14:6999–7004.
4. Shim M**,** Saab S. Severe hepatotoxicity due to Hydroxycut: a case report. *Dig Dis Sci.* 2009;54:406–409
5. Lobb A. Hepatotoxicity associated with weight-loss supplements: A case for better post-marketing surveillance. *World J Gastroenterol.* 2009;15:1786–1787.
6. Mozersky DO, Klonz K**,** Katz LM. The Problem: Liver toxicity following consumption of dietary supplement, Hydroxycut. Health Hazard Review Board FDA 2009. Available at: www.fda.gov/oc/opacom/hottopics/hydroxycut/HHE.pdf.
7. Jena BS, Jayaprakasha GK, Singh RP, Sakariah KK. Chemistry and biochemistry of (-)-hydroxycitric acid from *Garcinia*. *J Agric Food Chem.* 2002;50:10–22.
8. Jayaprakasha GK, Sakariah KK. Determination of organic acids in *Garcinia cambogia* (Desr.) by high-performance liquid chromatography. *J Chromatogr A.* 1998;806:337–339.
9. Antony JIX, Josan PD, Shankaranarayana ML. Quantitiative analysis of (–)hydroxy citric acid and (–)hydroxy citric acid lactone in *Garcina* fruits and *Garcinia* products. *J Food Sci Technol.* 1998;35:399–402.
10. Sergio W. A natural food, the Malabar Tamarind, may be effective in the treatment of obesity. *Med Hypothesis.* 1988;29:39–40.
11. Ohia SE, Opere CA, DeLay AM, Bagchi M, Bagchi D, Stohs SJ. Safety and mechanisms of appetite suppression by a novel hydroxycitric acid extract (HCA-SX). *Mol Cell Biochem.* 2002;238**:**89-103.
12. Shara M, Ohia SE, Yasmin T, et al. Dose- and time-dependent effects of a novel (–)-hydroxycitric acid extract on hepatic and testicular lipid peroxidation, DNA over a period of 90 days. *Mol Cell Biochem.* 2003;254**:**339–346.
13. Shara M**,** Ohia SE, Schmidt RE, et al. Physico-chemical properties of a novel (–)-hydroxycitirc 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.
14. Lowenstein JM. Effect of (–)-Hydroxycitrate on fatty acid systhesis by rat liver *in vivo*. *J Biol Chem.* 1971;246:629–632.
15. Sullivan AC, Triscari J, Hamilton JG, Miller ON, Wheatley JR. Effect of (–)-hydroxycitrate upon the accumulation of lipid in rat: I. Lipogenesis. *Lipids* 1974;9: 121–128.
16. Sullivan AC, Triscari J, Hamilton JG, Miller ON. Effect of (–)-hydroxycitrate upon the accumulation of lipid in rat: II. Appetite. *Lipids.* 1974;9:129–134.
17. Leonhardt M, Munch S, Westerterp-Plantenga M, Langhans W. Effects of hydroxycitrate, conjugated linoleic acid, and gur\ar gum on food intake, body weight regain, and metabolism after body weight loss in male rats. *Nutr Res.* 2004;24:659–669.
18. Leonhardt M, Balkan B, Langhans W. Effect of hydroxycitrate on respiratory quotient, energy expenditure, and glucose tolerance in male rats after a period of restrictive feeding. *Nutrition.* 2004;20:911–915.
19. 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.
20. 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.
21. Asghar M, Monjok E, Kouamou G, Ohia SE, Bagchi D, Lokhandwala MF. Super CitriMax (HCA-SX) attenuates increases in oxidative stress, inflammation, insulin resistance, and body weight in developing obese Zucker rats. *Mol Cell Biochem.* 2007;304:93-99.
22. 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.
23. Preuss HG, Rao SCV, Garis RI, et al. 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.
24. 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.
25. Preuss HG, Garis RI, Bramble JD, et al. Efficacy of a novel calcium/potassium salt of (–)-hydroxycitric acid in weight control. *Int J Clin Pharmacol Res.* 2005;25:133–144.
26. 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.
27. Downs BW, Bagchi M, Subbaraju GV, Shara MA, Preuss HG, Bagchi D. Bioefficiency of a novel calcium-potassium salt of (–)-hydroxycitric acid. *Mutat Res.* 2005;579:149–162.
28. Saito M, Ueno M, Ogino S, Kubo K, Nagata J, Takeuchi M. High dose *Garcinia cambogia* is effective in suppressing fat accumulation in developing male Zucker obese rats, but highly toxic to testis. *Food Chem Toxicol.* 2005;43:411–419.
29. Hayamizu K, Tomi M, Kaneko I, Shen M, Soni MG, Yoshino G. Effects of *Garcinia cambogia* extract on serum sex hormones in overweight subjects. *Fitoteripia.* 2008;79:255–261.
30. Mahendran P, Devi CS. Effect of *Garcinia cambogia* extract on lipids and lipoprotein composition in dexamethasone administered rats. *Ind J Physiol Pharmacol.* 2001;45:345–350.
31. 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. *Ind J Exptl Biol.* 2002;40:58–62.
32. Mahendran P, Vanisree AJ, Devi CS. The antiulcer activity of *Garcinia cambogia* extract against indomethacin-induced gastric ulcers in rats. *Phytother Res.* 2002;16:80–83.
33. Bousova I, Bacikova E, Dobrijevic S, Drsata J. Glycation of aspartate aminotransferase by methylglyoxal, effect of hydroxycitric and uric acid. *Mol Cell Biol.* May 18, 2009; (epub ahead of print).
34. Perennial Edible Fruits of the Tropics, An Inventory. US Department of Agriculture Handbook, No. 642; 1987.
35. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (Hydroxycitric acid) as a potential antiobesity agent. *J Amer Med Assoc.* 1998;280:1596–1600.
36. Kriketos AD, Thompson HR, Greene H, Hill JO. (–)-Hydroxycitric acid does not affect energy expenditure and substrate oxidation in adult males in a post-absorptive state. *Int J Obes Relat Metab Disorders.* 1999;23:867–873.
37. Lim K, Ryu S, Ohishi Y, et al. Shortterm (–)-hydroxycitrate ingestion increases fat oxidation during exercise in athletes. *J Nutr Sci Vitaminol.* 2002;48:128–133.
38. Lim K, Ryu S, Nho HS, et al.(–)-Hydroxycitric acid ingestion increases fat utilization during exercise in untrained women. *J Nutr Sci Vitaminol.* 2003;49:163–167.
39. Kovacs EMR, Westerterp-Plantenga MS. Effects of (–)-hydroxycitrate on net fat synthesis as *de novo* lipogenesis. *Physiol Behavior.* 2006;88:371–381.
40. Roy S**,** Rink C, Khanna S, et al. Body weight and abdominal fat gene expression profile in response to a novel hydroxycitric acid based dietary supplement. *Gene Express.* 2004;11:252–263.