



## Acute liver failure associated with *Garcinia cambogia* use

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### ABSTRACT

Millions of Americans regularly use herbal supplements, but many are unaware of the potential hidden dangers. Numerous supplements have been associated with hepatotoxicity and, indeed dietary/herbal supplements represent an increasingly common source of acute liver injury. We report a case of acute liver failure requiring liver transplantation associated with the use of *Garcinia cambogia*, a supplement widely promoted for weight loss. When patients present with acute hepatitis or liver failure from an unknown etiology, a careful history of supplement use should be performed.

**Key words.** Hepatotoxicity. Transplantation. Herbal supplements.

### INTRODUCTION

In the United States, the sale of herbal supplements represents billions of dollars in out-of pocket expenditures annually. Although millions of Americans regularly use herbal supplements, many are unaware of the potential hidden dangers. The false assumption that herbal supplements are 'natural' and therefore safe is a common misconception among consumers. Numerous supplements have been associated with hepatotoxicity and, indeed, dietary/herbal supplements represent an increasingly common source of acute liver injury.<sup>1</sup>

Herein we report a case of acute liver failure requiring liver transplantation probably due to *Garcinia cambogia*, an herbal supplement widely promoted for weight loss.

### CASE REPORT

A 52-year-old female was referred to our Hepatology Clinic for evaluation of jaundice and elevated serum aminotransferases. Approximately 2.5 weeks prior to her evaluation at our center, the patient visited her primary care physician for her annual exam and was found to have abnormal liver test results. Liver ultrasound to assess for the presence of gallstones was negative as was hepatitis A virus

screening. Subsequently, the patient was admitted to a local hospital for further evaluation and computerized tomography (CT) scan of chest, abdomen and pelvis was performed revealing a shrunken nodular liver consistent with collapsing necrosis.

Pertinent laboratory tests performed at an outside laboratory included:

- Total bilirubin 10.1 mg/dL.
- Aspartate aminotransferase (AST) 723 u/L.
- Alanine aminotransferase (ALT) 568 u/L.
- International normalized (INR) ratio of prothrombin time 2.03, and
- Platelet count 60,000.

Serum creatinine was within normal limits. Calculated Model for End Stage Liver Disease (MELD) score based on these lab tests was 23. The patient's past medical history was unremarkable. She had recently started taking the herbal supplement, *Garcinia cambogia* (USA Nutra Labs) 1,000 mg (2 capsules) daily to facilitate weight loss. The patient purchased a bottle containing 60 capsules and continued to take *Garcinia cambogia* until she began experiencing decreased appetite, worsening fatigue and intermittent confusion. She discontinued the supplement, after using a

total of approximately 50 capsules, shortly after the initial onset of symptoms. The patient denied any history of blood transfusion, family history of liver disease, or intravenous drug use. Additionally, she denied any history of alcohol abuse. Her medication/supplement list at the time of evaluation also included a topical hormone cream containing Bi-Estrogen 2.5/progesterone 30/DHEA 2.5, melatonin, dicyclomine as needed for abdominal pain, and dancing willow herbs, a topical antifungal nail oil. The patient had been taking melatonin and dicyclomine for at least a year prior to her symptoms, and using the topical hormonal cream and antifungal nail oil for more than a year prior to her evaluation in our institution.

Initial physical examination was unremarkable, with the exception of mild abdominal distention, and jaundice; vital signs were all within normal limits. Laboratory tests revealed:

- Serum creatinine 0.7 mg/dL.
- Total bilirubin 8.5 mg/dL.
- Direct bilirubin 4.4 mg/dL.
- AST 1,001 u/L.
- ALT 645 u/L.
- Alkaline phosphatase 140 u/L.
- INR 3.24, and
- Platelet count 67,000.

MELD score based on lab tests was 28. Urine drug toxicology tests were all negative. Hepatitis serologies revealed the following:

- HBsAg negative.
- IgM anti-HBc negative.
- Anti-HBs was > 1,000 mIU/mL.
- IgM anti-HAV was negative.
- Anti-HCV negative.
- HCV-RNA by RT/PCR negative.
- IgG anti-HEV negative.
- IgM anti-HEV negative.

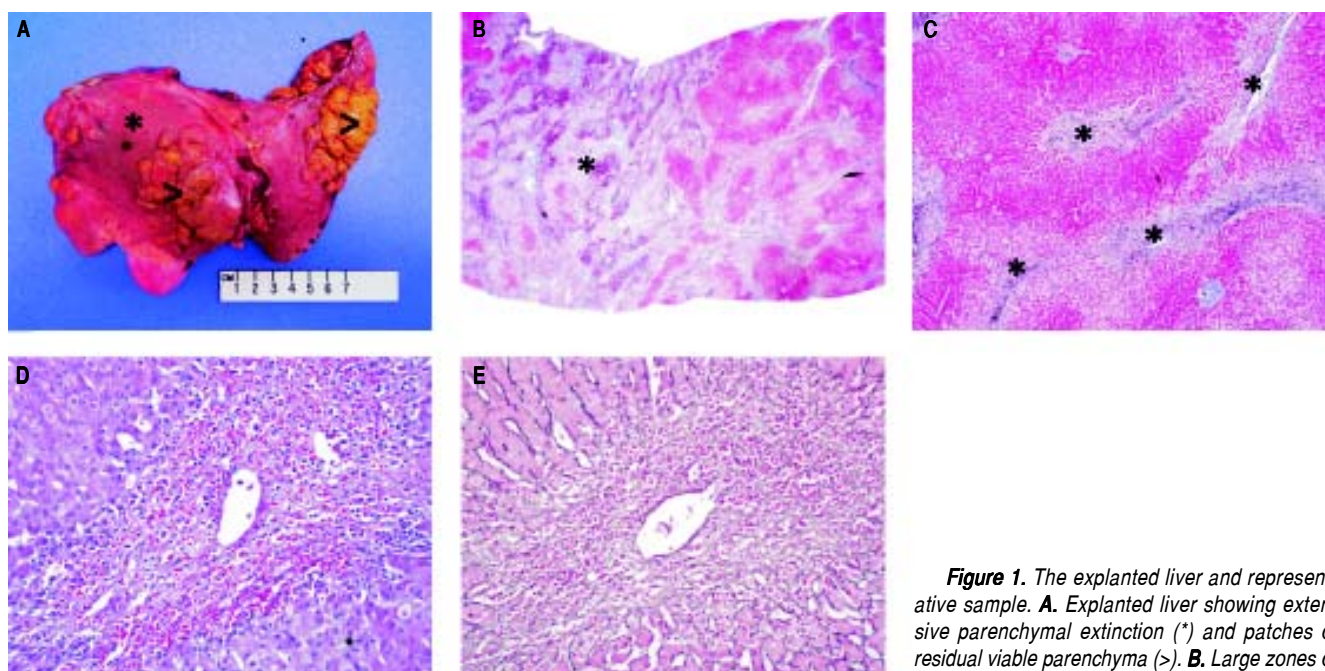
Results of testing for other viral etiologies included:

- IgG anti-CMV positive.
- IgM-anti-CMV negative.
- CMV DNA by PCR was negative.
- IgG anti-EBV VCA positive.
- IgM anti-EBV VCA negative.
- EBV DNA by PCR was negative.
- IgG anti-HSV 1/2 negative.
- IgM anti-HSV 1/2 negative.
- IgG anti-measles negative.
- IgM anti-measles negative.

Autoimmune markers (anti-smooth muscle antibody, anti-mitochondrial antibody, antinuclear antibody, and anti-liver kidney microsome 1 antibody) were negative. Alpha-1-antitrypsin phenotyping, serum ceruloplasmin, and serum alpha-fetoprotein were all within normal limits and human immunodeficiency virus testing was negative. Abdominal CT again revealed moderate ascites and a shrunken nodular liver consistent with collapsing necrosis. No focal mass was visible, common bile duct diameter was normal and hepatic vasculature was patent with normal flow.

Liver biopsy performed at an outside institution 5 days prior to our initial evaluation revealed severe acute hepatitis with confluent necrosis and massive parenchymal collapse; very few viable hepatocytes remained. The inflammatory infiltrate was mixed including predominantly lymphocytes with a smaller population of plasma cells, neutrophils and rare eosinophils. Differential diagnosis based on histopathology findings primarily included viral hepatitis, autoimmune hepatitis, and drug-induced liver injury. Due to worsening liver test abnormalities and hepatic encephalopathy the patient was admitted to the hospital for close monitoring and management of her worsening acute liver injury. Pertinent laboratory tests obtained on the day of hospital admission included total bilirubin 11.1 mg/dL, direct bilirubin 5.2 mg/dL, AST 990 u/L, ALT 655 u/L, ammonia 88 mcg/dL, INR 4.32 and serum creatinine 0.8 mg/dL. Despite supportive management, the patient continued to have worsening coagulopathy, rising bilirubin and hepatic encephalopathy. Her condition continued to deteriorate, her hemodynamic status was labile and upon development of hypoglycemia, despite supplemental dextrose administration, she was transferred to the Intensive Care Unit. The patient's MELD score was 40 and she was ultimately listed as Status 1 at the United Network for Organ Sharing (UNOS).

One day after listing, approximately fifty days after initial onset of symptoms, the patient underwent successful deceased donor orthotopic liver transplantation. Post-operative course was uneventful, liver tests continued to improve, INR normalized and the patient was discharged on postoperative day 7. The explanted liver weighed 433 g, and showed extensive sub-acute parenchymal extinction with a zone III distribution in more preserved areas (Figure 1). The liver parenchyma demonstrated central congestion throughout and there was very little normal-appearing liver parenchyma with the exception of the lateral portion of the right lobe. We concluded that the most probable etiology of the acute liver failure in this patient was the herbal supplement, *Garcinia cambogia*, that she had taken for weight loss. We applied the CIOMS scale<sup>2,3</sup> to the medications and herbal supplement that the patient was taking prior to the onset



**Figure 1.** The explanted liver and representative sample. **A.** Explanted liver showing extensive parenchymal extinction (\*) and patches of residual viable parenchyma (>). **B.** Large zones of subacute parenchymal extinction (\*). Trichrome, 40 X. **C.** In residual viable areas, a zone III distribution of injury is apparent (\*). Trichrome, 40 X. **D.** Zone III region showing subacute hepatocyte dropout around a central vein. H&E, 200 X. **E.** Loss of the normal reticulin network and hepatic plates in areas of dropout. Reticulin, 200 X.

12.5 X. **C.** In residual viable areas, a zone III distribution of injury is apparent (\*). Trichrome, 40 X. **D.** Zone III region showing subacute hepatocyte dropout around a central vein. H&E, 200 X. **E.** Loss of the normal reticulin network and hepatic plates in areas of dropout. Reticulin, 200 X.

of her symptoms; the CIOMS score for *Garcinia cambogia* was 7 which establishes it as a probable etiology. The other two, melatonin and dicyclomine, that were taken for a year or more prior to the onset of symptoms, were unlikely etiologies according to the CIOMS scale.

## DISCUSSION

The popularity of dietary supplements in the United States is readily apparent. With the prevalence of obesity rising in the United States, many have looked to supplements to facilitate weight loss. In one survey report, an estimated 15.2% of adults (women 20.6%, men 9.7%) in the United States reported having ever used a weight-loss supplement and 8.7% reported using an herbal supplement for weight loss within the past year.<sup>4</sup>

The association between herbal supplements and hepatotoxicity is of particular concern.

Numerous herbal supplements have been implicated as a cause of acute liver injury including severe liver injury resulting in death or requiring liver transplantation in some cases. For example, green tea extract supplements promoted for weight loss have been associated with acute liver failure requiring liver transplantation.<sup>5</sup> In addition, in 2009, the United States Food and Drug Administration (US FDA) warned consumers about Hydroxycut (Inova Health Sciences), a product that contained *Garcinia cambogia* at the time as well as several other

ingredients, based on reports of liver damage including at least 1 death.<sup>6,7</sup> More recently, in 2013 the US FDA along with the Centers for Disease Control and Prevention, the United States Department of Defense Armed Forces Health Surveillance Center, and state and local health officials investigated an outbreak of non-viral hepatitis that began in Hawaii. During this outbreak, multiple cases of acute liver failure or acute hepatitis were reported in patients who were taking OxyElite Pro (USP Labs, LLC), an herbal supplement promoted for weight loss and body-building.<sup>8,9</sup>

The *Garcinia cambogia* supplement taken by the patient in this report was manufactured by USA NutraLabs and contains calcium (50 mg), chromium (200 mcg), potassium (50 mg), and *Garcinia cambogia* extract (936 mg) fruit rind with 60% hydroxycitric acid (HCA) per serving (2 capsules). Hydroxycitric acid contained in the rind of the *Garcinia cambogia* fruit is purported to be the active component. HCA, an inhibitor of the citrate cleavage enzyme (ATP citrate lyase) blocks *de novo* synthesis of fatty acids, and reportedly increases hepatic glycogen synthesis, reduces food intake by suppressing appetite and decreases body weight gain.<sup>10</sup> However, in a randomized controlled trial involving 135 participants, treatment with *Garcinia cambogia* (HCA) for 12 weeks failed to produce significant weight loss and fat mass loss beyond that observed with placebo.<sup>11</sup> Furthermore, a study that analyzed 5 systemic reviews and metaanalyses as well as 25 additional published trials evaluating dietary sup-

plements, such as *Garcinia cambogia*, for weight loss concluded that the evidence for most supplements is not convincing and none of the dietary supplements reviewed could be recommended for use.<sup>12</sup>

A second, more recent systematic review and meta-analysis reported that *Garcinia* extracts/HCA can cause short-term weight loss, but the magnitude of the effect is small and the clinical relevance is uncertain.<sup>13</sup>

Liver injury associated with drugs or herbal supplements continues to be a diagnosis by exclusion. Dalton, *et al.*<sup>14</sup> and more recently, Davern, *et al.*<sup>15</sup> have pointed out that a small proportion of cases of acute liver injury that are suspected to be drug induced are really caused by HEV infection. In our patient, HEV serologies were negative ruling out HEV infection as an etiology. We did not perform HEV-RNA determination in either serum or liver explant.

In summary, *Garcinia cambogia* was the most probable etiology for the progressive, acute liver failure that ultimately required liver transplantation in our patient. Consumers and health care providers need to be aware of the potential risks associated with herbal supplements.

Importantly, when patients present with acute hepatitis or liver failure from an unknown etiology, a careful history of dietary or herbal supplement use should be performed.

## ABBREVIATIONS

- **ALT:** alanine aminotransferase.
- **AST:** aspartate aminotransferase.
- **CT:** computerized tomography.
- **DHEA:** dehydroepiandrosterone.
- **HCA:** hydroxycitric acid
- **INR:** international normalized ratio.
- **MELD:** Model for End-Stage Liver Disease.
- **UNOS:** United Network for Organ Sharing.
- **US FDA:** United States Food and Drug Administration.

## DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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