

Hepatotoxicity Due to Hydroxycut: A Case Series

Tse-Ling Fong, MD¹, Karl C. Klontz, MD², Alejandro Canas-Coto, MD³, Steven J. Casper, PhD², Francisco A. Durazo, MD^{4,8}, Timothy J. Davern II, MD^{5,8}, Paul Hayashi, MD⁶, William M. Lee, MD^{3,8} and Leonard B. Seeff, MD⁷

- OBJECTIVES:** Muscletech Hydroxycut (Iovate Health Sciences Research, Oakville, Ontario, Canada) was a popular weight-loss supplement that was recalled by the manufacturer in May 2009 on the basis of reports of hepatotoxicity associated with this supplement. We sought to characterize the clinical presentation of Hydroxycut-associated liver injury and to adjudicate these cases for causal association with Hydroxycut.
- METHODS:** We assessed the causality and grading of severity of liver injury using methodology developed by the Drug-Induced Liver Injury Network (DILIN) study.
- RESULTS:** Eight patients who developed liver injury after taking Hydroxycut treated at different medical centers were identified. All were hospitalized, and three of eight patients required liver transplantation. Nine other cases with adequate clinical information were obtained from the FDA MedWatch database, including one fatal case of acute liver failure. Usual symptoms were jaundice, fatigue, nausea, vomiting, and abdominal pain. Most patients exhibited a hepatocellular pattern of injury. Adjudication for causality revealed eight cases as definite, five highly likely, two probable, and two were considered to be possible.
- CONCLUSIONS:** Hydroxycut has been clearly implicated as a cause for severe liver injury that may lead to acute liver failure and death. Weight-loss supplements represent a class of dietary supplements that should be regarded as capable of causing severe hepatic toxicity when the usual causes of identified liver injury cannot be otherwise elucidated.

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INTRODUCTION

Under the Dietary Supplement Health and Education Act of 1994, dietary supplements do not require previous approval by the Food and Drug Administration (FDA) to be sold on the market. Until recently, regulation of supplements by the FDA was limited to monitoring of safety on the basis of voluntary adverse event reporting, but as of 22 December 2007, dietary supplement manufacturers have been required to submit through MedWatch reports of serious adverse events linked to the use of dietary supplements in the United States. (1). In 2002, a weight-loss supplement called Muscletech Hydroxycut (Iovate Health Sciences Research, Oakville, ON), marketed by the manufacturer as a “fat burner,” began to be heavily advertised for sale in retail chains and over the Internet. Indeed, during 2008, more than 9 million units of Hydroxycut were sold in the United States (US) (2).

Shortly after its launch, the first report of liver injury from the product appeared (3), followed by five additional publications (4–8) that together detailed a total of 11 persons who developed severe liver injury from Hydroxycut, all of whom recovered. In the past 7 years, the present authors have seen another eight cases of unusually severe liver injury ascribed to Hydroxycut. Moreover, by the end of April 2009, the FDA had received 23 additional reports of severe liver injury attributed to Hydroxycut, submitted through the voluntary reporting MedWatch system, and more recently, a fatal case was reported to them through MedWatch. Using the Freedom of Information Act (FOIA), we obtained redacted versions of the reports of these 24 cases. On 1 May 2009, the FDA issued a warning to the public to stop using Hydroxycut products, which was followed by a voluntary recall of all its products by the manufacturer (9).

¹Division of Gastrointestinal and Liver Diseases, University of Southern California, Los Angeles, California, USA; ²Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Bethesda, Maryland, USA; ³Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA; ⁴Division of Digestive and Liver Diseases, University of California, Los Angeles, Los Angeles, California, USA; ⁵Division of Gastroenterology, University of California, San Francisco, San Francisco, California, USA; ⁶Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; ⁷Liver Diseases Research Branch, Division of Digestive Diseases and Nutrition, National Institutes of Health, Bethesda, Maryland, USA; ⁸The National Institute of Diabetes and Digestive and Kidney Diseases Drug-Induced Liver Injury Network Study Group. **Correspondence:** Tse-Ling Fong, MD, Division of Gastrointestinal and Liver Diseases, University of Southern California, Keck School of Medicine, 1510 San Pablo Street, 2/F, Los Angeles, California 90033, USA. E-mail: tselingf@usc.edu

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This report describes 17 thus-far unpublished cases of hepatotoxicity attributed to Hydroxycut; eight consist of patients who became ill after ingesting Hydroxycut and who were seen by the present authors at their respective hospitals between September 2002 and February 2009 (hereafter referred to as “clinical center patients”). Added to these are 9 of the 24 cases from the FDA MedWatch database, from whom sufficient clinical details were available to permit causality assessment (hereafter referred to as “FDA cases”). Each developed acute liver injury that was more severe than that described in previously reported cases; one patient died as a result of hepatotoxicity and three required liver transplantation. The aim of this report was to characterize the clinical presentation of these 17 cases of Hydroxycut-associated liver injury.

METHODS

Detailed clinical data were extracted from medical records of eight previously healthy patients who presented at various academic medical centers in the United States when they developed severe acute hepatic injury after taking Hydroxycut. Clinical information on the 24 FDA cases obtained through the FOIA request was reviewed to determine that nine contained sufficient clinical data for further analysis. To the best of our knowledge, all 17 patients were taking the dietary supplement at the doses suggested by the manufacturer. All available clinical and laboratory

data were then abstracted and utilized for further independent in-depth assessment of causality and grading of severity of liver injury using the guidelines developed by the Drug-Induced Liver Injury Network (DILIN) study (10).

Causality assessment and grading of severity were performed independently by four of the authors, two from academia (WML, T-LF), one from the FDA (KK), and one from the National Institutes of Health (LBS). Because there is no diagnostic marker for drug-induced liver injury, assessing causality using clinical acumen is challenging, even for experts, as it is an inherently subjective approach. To bring some uniformity to this issue, we utilized the five categories developed in the DILIN study to assess the percentage likelihood of causality: 1=Definite (>95%), 2=Highly Likely (75–95%), 3=Probable (50–74%), 4=Possible (25–49%), 5=Unlikely (<25%), and 6=Insufficient data. Severity of liver injury was graded using the criteria developed and published by the DILIN study (10). The Roussel Uclaf Causality Assessment Method was initially also used to assess causality. However, this method was abandoned because of significant variability in scoring and difficulty in reaching consensus, a result that has been previously noted (11,12).

On completion of the initial assessment by the four reviewers, the results were submitted to the coordinating center (UT Southwestern) where the data were compiled for further analysis. All scores were then redistributed to the individual reviewers

Table 1. Clinical characteristics of 8 clinical center cases of Hydroxycut toxicity

| Variable | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 |
|------------------------------------|----------------------------|---|--|---|--|-----------------------------------|---|----------------------------|
| Past medical history | None ANA 1:160 | None | None | None | Obesity ANA 1:20 SMA 1:40 treated with prednisone | None ANA 1:320 SMA positive | Obesity ANA initially negative, later became 1:160 Actin antibody 30 U/ml | None |
| Duration of Hydroxycut use (weeks) | 52 | 8 | 6 | 4 | 104 | 8 | 8 | 4 |
| Peak ALT level | 1,450 | 3,223 | 2,729 | 2,258 | 2,385 | 2,635 | 3,099 | 5,396 |
| Peak AST level | 602 | 1,644 | 1,891 | 1,782 | 2,615 | 1,970 | 3,005 | 4,693 |
| Peak bilirubin level (mg/dl) | 45 | 40.5 | 33.3 | 37.0 | 18.8 | >30 | 11.1 | 33.6 |
| Peak alkaline phosphatase | 226 | 141 | 180 | 167 | 139 | 203 | 144 | 280 |
| Peak prothrombin INR | 6.45 | 4.3 | 1.43 | 1.66 | 1.3 | 1.2 | 1.9 | 3.71 |
| Outcome | Liver transplant on day 17 | Liver transplant on day 35 | Recovered | Recovered | Recovered | Recovered | Recovered | Liver transplant on day 40 |
| Symptoms | Nausea | Nausea, vomiting, fatigue, and abdominal pain | Nausea, vomiting, itching, and fatigue | Nausea, vomiting, fatigue, and abdominal pain | Nausea, vomiting, fatigue, and abdominal pain | Vomiting and fatigue | Nausea and abdominal pain | Nausea, vomiting, fatigue |
| Histology | Massive hepatic necrosis | Sub-massive hepatic necrosis | | | Acute hepatitis with cholestasis | Acute hepatitis with cholestasis | | Massive hepatic necrosis |

for comparison and deliberation. This was followed by a teleconference in which any discrepancies in the DILIN scores were discussed and reconciled, resulting in a final consensus score.

RESULTS

Clinical characteristics and severity of liver disease among the eight clinical center patients

A summary of the demographical and clinical features of the eight patients (six male and two female) is shown in **Table 1**. Their mean age was 30.9 (range 17–54) years; six patients were Hispanic, one Caucasian, and one Asian. None of the patients had any past medical history of relevance, any alcohol abuse, or any parenteral risk factors. Serologies for hepatitis A, B, and C, Epstein–Barr virus, and cytomegalovirus infection were uniformly negative. Patient weights or BMI data were not available.

Four patients (three male/one female) were positive for anti-nuclear and/or anti-smooth muscle antibodies (patients 1, 5, 6, and 7) but all four, as well as the four without these autoimmune markers, had normal serum globulin levels. One of the four with the autoimmune antibodies progressed to acute liver failure and required liver transplant; the explanted liver did not show features suggestive of autoimmune hepatitis. Two patients with autoimmune markers recovered completely without corticosteroid treatment, although the fourth patient was treated briefly with corticosteroids. Thus, they did not satisfy these and other requirements for a diagnosis of autoimmune hepatitis using either the International Autoimmune Hepatitis Group criteria (13) or the simplified criteria (14). The latency period, or interval between initiation of ingestion of Hydroxycut and onset of symptoms, ranged from 1 to 8 (median 6) weeks, with two outliers who had taken the supplement for 52 and 104 weeks, although intermittently. Fatigue occurred in six of the eight cases. All patients experienced nausea and/or vomiting. Abdominal pain was present in four patients. Jaundice was present in all eight patients; peak serum bilirubin levels ranged from 11.1 to 45 (mean 31.3) mg/dl. All eight patients exhibited a hepatocellular pattern of liver injury ($R > 5$) (11). Peak alanine aminotransferase activities (ALT) ranged from 1,450 to 5,396 (mean 2,911) U/l; aspartate aminotransferase activities (AST) ranged from 602 to 4,693 (mean 2,225) U/l; and alkaline phosphatase levels ranged from 139 to 280 (mean 185) U/l. No fever, rash, or eosinophilia was seen in any of these patients. None developed renal failure. Biopsy tissue was available for four of the eight patients. Two came from explanted livers, and revealed massive (**Figure 1a**) or submassive hepatic necrosis. Liver biopsies taken from two patients who recovered spontaneously showed severe acute hepatitis with cholestasis (**Figure 1b** and **c**).

All eight patients had been hospitalized. Three patients had signs of liver failure and required liver transplantation, fulfilling the DILIN criteria for grade 5 severity (death or transplantation). The other five included three with no signs of liver failure (grade 3) and two with prolonged PT/INR (grade 4). All three transplanted patients are well, with excellent allograft

function and normal liver tests at 44 and 16 months after transplantation, respectively, in the two patients with long-term follow-up.

Clinical characteristics and severity of liver disease among the nine FDA cases

Data from the nine cases that had been submitted to the FDA with adequate information for review are summarized in **Table 2**. Six were female. Their mean and age ranges were similar to those of the eight clinical center patients. Clinical data were not complete in all nine MedWatch reports. The median latency was similar to the eight clinical center cases, as were the peak AST and ALT levels, but the mean peak bilirubin level was significantly lower among these nine FDA cases, 20.6 vs. 31.3 mg/dl. All nine FDA cases were hospitalized, jaundiced, and had elevated aminotransferase levels.

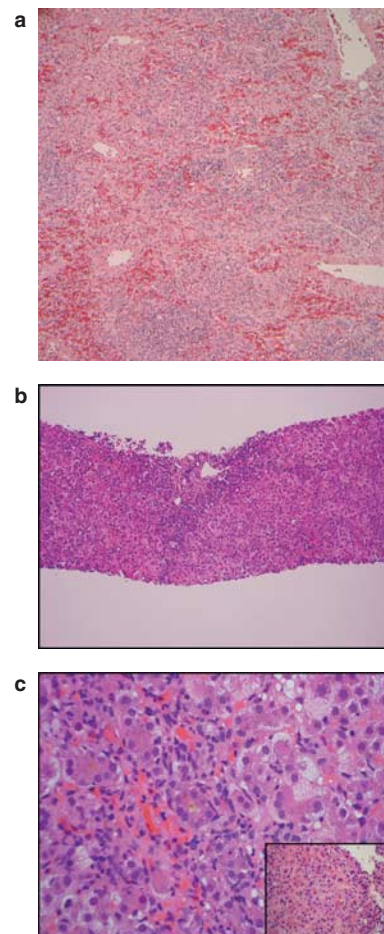


Figure 1. (a) Liver biopsy for patient 1. Residual hepatic parenchyma with irregularly widened portal areas, mixed inflammatory infiltrates, hepatocellular swelling, and spotty hepatocellular dropout. Numerous foci representative of previous bridging necrosis are shown, with bridging of portal areas by metaplastic biliary structures (hematoxylin and eosin (H&E), $\times 40$). (b and c) Low-power view of needle liver biopsy for patient 5. Panlobular hepatic inflammatory infiltrate and cholestasis (H&E, $\times 40$). Higher power view of the same biopsy: a mononuclear, neutrophilic, and eosinophilic portal inflammatory infiltrate is seen with circumferential interface injury and extensive metaplastic ductular proliferation at the edge of the expanded portal tract (H&E, $\times 200$).

Table 2. Summary of clinical characteristics of nine FDA cases of Hydroxycut-associated liver injury

| Characteristic | n ^a | Range | |
|---------------------------------------|----------------|-----------------|-------------------------|
| Mean age (years) | 9 | 30.4 | 23–51 (median 27) |
| Sex | 9 | 3 Male/6 female | |
| Latency (weeks) | 6 | 6.5 | 2–13 |
| Abdominal pain | 7 | 6/7 | |
| Nausea/vomiting | 7 | 7/7 | |
| Fatigue | 5 | 4/5 | |
| Jaundice | 9 | 9/9 | |
| Peak ALT (U/l), mean | 8 | 2,538 | 756–3,131 (median 2181) |
| Peak AST (U/l), mean | 9 | 1,671 | 114–2,783 (median 2109) |
| Peak alkaline phosphatase (U/l), mean | 5 | 421 | 176–1,147 (median 257) |
| Peak total bilirubin (mg/dl), mean | 8 | 20.6 | 3–41.4 (median 14.7) |
| <i>Pattern of liver injury</i> | | | |
| Hepatocellular ($R > 5$) | 4/5 | | |
| Cholestatic ($R < 2$) | 1/5 | | |

^aNumber of case reports with specific pertinent data.

One FDA case was noted to be anti-HCV positive without further confirmatory data. Another case presented with a cholestatic pattern of liver injury; AST level was 114 U/l, total bilirubin was 7.4 mg/dl, and alkaline phosphatase was 1147 U/l. DILIN severity grade 3 was assigned to the eight FDA cases who recovered and severity grade 5 was assigned to the fatal case.

The single fatal case was a 20-year-old Hispanic male with no previous significant medical problems, who began taking Hydroxycut as part of his exercise routine. After 13 weeks, he developed jaundice, fatigue, and nausea. His initial blood test revealed acute hepatitis (ALT 2,323 U/l, AST 1,391 U/l, total bilirubin 10.7 mg/dl, alkaline phosphatase 91 U/l). Serologies for hepatitis viruses A, B, and C were negative. Prothrombin time was not obtained at the initial evaluation nor was the history of Hydroxycut use elicited. During the ensuing 3 weeks, he became increasingly lethargic and jaundiced. On admission, he was encephalopathic and his PT/INR was > 13; a history of Hydroxycut use was obtained. The following day, he underwent exploratory laparotomy for liver transplantation, but was found to have intestinal infarction. Liver transplantation was aborted and the patient expired shortly afterward. His autopsy revealed “acute fulminant hepatitis.”

Causality assessment

On initial evaluation, complete agreement of causality scores was reached among all reviewers in four of the eight clinical center cases and in one of the nine FDA cases. The scores among the 12 cases without unanimity differed by only one stratum in all but one case, but the differences were reconciled without difficulty

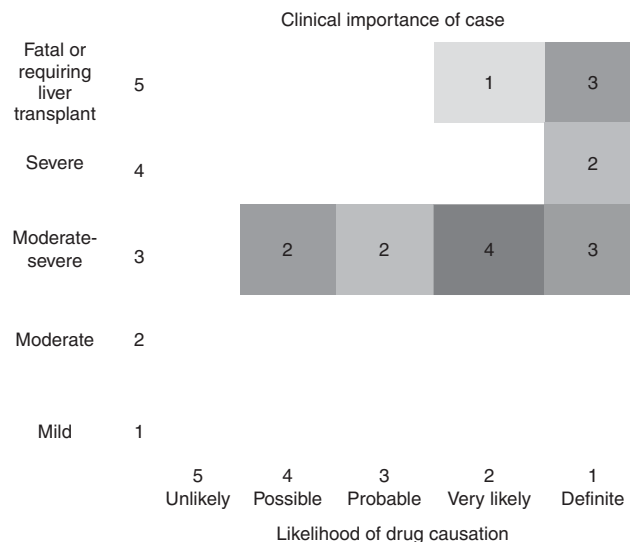


Figure 2. Five-by-five table of likelihood and severity using DILIN criteria (9) to adjudicate 17 previously unreported cases of hepatotoxicity due to Hydroxycut (modeled after a matrix developed by John Senior, MD, FDA).

in all 17 cases after further discussion. The final causality assignments are shown in **Figure 2**. Eight cases were considered definite, five highly likely, two probable, and two (which included the two FDA cases: one patient who was anti-HCV positive and another patient with the cholestatic liver injury) were considered to be possibly related.

DISCUSSION

The 17 cases of Hydroxycut-associated liver injury presented here were similar to previous reports in having, for the most part, hepatocellular injury. However, they showed a greater degree of severity of injury; all cases were hospitalized, three required liver transplantation and there was one fatality due to acute liver failure. Among the eight clinical center patients, it is notable that six of the eight were Hispanic. It is unclear whether this is due to a genetic predisposition or to the fact that these patients were from Southwestern United States (California, New Mexico, and Texas) where Hispanics account for a relatively higher proportion of the population than elsewhere in the United States, or whether the high prevalence of obesity among Hispanic Americans leads to more frequent use of weight-loss supplements. Ethnicity information was lacking for some of the FDA patients. Excluding the two outlier patients who were taking Hydroxycut intermittently for 52 and 104 weeks, respectively, the mean latency period among these cases was 6.4 weeks compared with the 7.8 weeks among the previously reported patients. Also in agreement with the previously reported cases, all patients were symptomatic, the majority describing fatigue, nausea/vomiting, and abdominal pain. None of the patients described here had been subjected to a rechallenge with the product, although some had taken it intermittently as noted.

With the exception of one of our cases and one previously reported case (5), the predominant pattern of liver injury was severe

hepatocellular injury with marked elevation of aminotransferase levels and minimal abnormalities in alkaline phosphatase levels and histological features in five patients showing marked hepatocellular necrosis and injury. It is intriguing that four of the eight persons tested for autoimmune markers were positive for antinuclear antibodies at the time of the acute liver injury. Whether this was a consequence of the herbal product, a transient phenomenon associated with the acute injury, or represented identification of previously unrecognized autoimmune hepatitis, is not entirely clear. It seems unlikely that preexisting autoimmune hepatitis was responsible, as the cases were mostly male and the findings did not conform to the criteria of the International Autoimmune Hepatitis group (13). Conceivably, Hydroxycut might have induced an immunological response manifesting as autoimmune-like liver disease (15), such as has been noted previously with other drugs that include oxyphenisatin, minocycline, and nitrofurantoin (16–18).

The formulation of Hydroxycut has changed in recent years. The earliest reported cases of acute liver injury related to Hydroxycut were part of a case series of patients who had developed severe hepatitis after taking various supplements containing ephedra, also called Ma Huang, a plant substance the natural ingredient of which is ephedrine (3). In 2004, the sale of supplements containing ephedra was banned by the FDA because of evidence linking ephedra to cardiovascular, neuro-psychiatric, and gastrointestinal side effects (19). However, even though Ma Huang was removed from the formulation of Hydroxycut in 2003, nine subsequent cases of Ma Huang-free Hydroxycut-associated hepatotoxicity were reported, all of whom spontaneously recovered (4–8). Despite these reports, Hydroxycut remained a popular and highly advertised dietary supplement for weight loss that could be purchased in retail stores and over the Internet. On 1 May 2009, following a public warning issued by the FDA regarding the risk of severe liver injury associated with ingestion of Hydroxycut, its manufacturer recalled all Hydroxycut products (9).

Assigning causality in cases of dietary supplement-related hepatotoxicity is more complex than that associated with conventional prescription drugs, as individuals using dietary supplements often ingest multiple products and the contents of each product may include many ingredients that are poorly characterized. Doses are not certain, as there is less oversight of these products than of standard prescription medications. Because of these additional challenges, we sought to rigorously adjudicate case histories and to assign causality scores using the methods used in the DILIN study.

The specific ingredient or ingredients in Hydroxycut responsible for causing injury remain uncertain. Even with the removal of Ma Huang (ephedra), many formulations still contain other ingredients that may present a health concern, such as *Garcinia cambogia*, *Cissus quadrangularis*, caffeine, and green tea extract.

Garcinia is a tree found in Asia and Africa, the fruit extract of which is used as a supplement ingredient. There are some studies in published literature that examine its use, but there is no detailed study or evidence that supports the safety of this ingredient. Similarly, *Cissus* is a plant, the consumption of which is geographically limited, and there is some evidence of its use but no safety studies;

rather, there is an article that presents the toxic effects of this plant on goats and sheep (20). Caffeine has been the subject of many published articles, but appropriate consumption levels and long-term effects, including adverse effects on the liver, still remain equivocal. The safety of green tea extracts was systematically reviewed by the US Pharmacopeia Dietary Supplements Information Expert Committee (21). In their assessment of French–Spanish reports, Sarma *et al.* (21) analyzed 13 cases of acute liver injury associated with Exolise (containing hydro-alcoholic extract of green tea), which resulted in acute liver failure, one patient requiring liver transplantation (22), and four other cases of liver injury associated with Tealine (aqueous extraction of green tea). The clinical presentation, latency, pattern, and degree of hepatic biochemical injury of the aforementioned cases of hepatotoxicity related to green tea extracts resemble other cases of Hydroxycut-associated liver injury (3–8,22–25).

Toxicity from other constituents contained in Hydroxycut, some possibly not identified, cannot be ruled out as a cause of liver injury. Chromium polynicotinate, which is found in Hydroxycut, was reported to cause acute hepatocellular liver injury in a patient who also took various plant extracts including *Garcinia cambogia* (26). There is even concern for supplement products in general that liver injury may come not from listed ingredients but from contaminants such as lead, mercury, or arsenic (27–29). There are indeed reports of several other herbals and/or weight-loss products purchased through the Internet that are known to have caused liver injury (30). It is also important to keep in mind that the safety of ingredients may vary because of the methods of extraction and preparation and also because of the possibility of interaction between ingredients that may lead to adverse events.

Hydroxycut represents the latest dietary supplement in a series of herbal products documented to cause severe liver injury (31–33). Given that MedWatch is a largely voluntary reporting system, we believe that the cases of liver toxicity related to Hydroxycut described here are a fraction of those that have occurred. To promote the reporting of serious adverse events, the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 requires that, as of 22 December 2007, dietary supplement manufacturers submit, through MedWatch, reports of serious adverse events linked to the use of dietary supplements in the United States. Reports may be submitted to Medwatch online (www.fda.gov/medwatch/report.htm), or, alternatively, a form from the back of the Physicians Desk Reference or obtained from www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf can be mailed to FDA (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), faxed to FDA (1-800-FDA-0178), or its details conveyed by telephone to FDA (1-800-FDA-1088).

In conclusion, Hydroxycut has been clearly implicated as a cause of liver injury, largely hepatocellular in nature, and severe enough to have culminated in the need for hospital admission among all 17 identified cases, four of whom died or required liver transplantation. The responsible toxic ingredient is not entirely certain, but may be the consequence of the presence of *Camellia sinensis* in the product.

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CONFLICT OF INTEREST

Guarantor of the article: Tse-Ling Fong, MD.

Specific author contributions: Tse-Ling Fong, Alejandro Canas-Coto, William Lee, Karl Klontz, Steven Casper, and Leonard Seeff were responsible for study design, data collection, and analysis and preparation of the final paper; Tse-Ling Fong, William Lee, Karl Klontz, and Leonard Seeff performed the causality assessment; Tse-Ling Fong, Alejandro Canas-Coto, William Lee, Francisco Durazo, Timothy Davern, and Paul Hayashi recruited patients.

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Potential competing interests: None.

Study Highlights**WHAT IS CURRENT KNOWLEDGE**

✓ Hydroxycut, a weight-loss supplement, has been reported to cause nonfatal hepatotoxicity.

WHAT IS NEW HERE

✓ We applied the newly developed Drug-Induced Liver Injury Network guidelines for assessment of causality and severity in 17 new cases of Hydroxycut liver injury.

✓ We report four cases of severe Hydroxycut-associated acute liver failure that resulted in death or need for liver transplantation.

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