Chemical Analysis of Weight Loss Herbal Supplement Safe Lean™ Associated With Acute Liver Injury – A Concern for Spurious Drug, Misbranding and Adulteration

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Liver injury due to herbal and dietary supplements are well described in literature and its incidence has been on the rise in the past decade. Labelling an herbal product as non-medicinal and as a supplement precludes protocols needed for testing, trials and marketing criteria. This has led to rampant use of clinically unproven multi-herb-based drugs use for a myriad of lifestyle diseases. In this report, we discuss a new dietary weight loss supplement, Safe Lean™ that was found to be the cause of liver injury in a young obese woman, that resolved after discontinuation, and discuss current literature on component, toxicology and chemical analysis of the offending drug. (J Clin Exp Hepatol 2018;8:471–473)

Herbal and Dietary Supplements (HDS) used for weight loss have been directly implicated in many cases of liver injury ranging from acute hepatitis to acute liver failure requiring liver transplantation or leading to death. Herbal and dietary supplements are considered 'food-grade' and are regulated differently than conventional pharmaceuticals. In medical literature, major weight loss supplements that are reported to be associated with severe liver injury include green tea extracts, conjugated linoleic acid, usnic acid containing products (such as LipoKinetix®, Lipolyz® and Somalyz®), Herbalife® products, Hydroxycut, Dimethylamylamine (DMAA; OxyELITE®), Gota Kolu (*Centella asiatica*), Ma-Huang containing products (such as Pro-Lean®), Sennomotokounou (Chinese 11 herb mixture) and Exolise®, a weight loss supplement, which was withdrawn from the market in France and Spain due to hepatotoxicity.[1,2] In most cases, liver injury was found to be due to an active metabolite of the disclosed main ingredient where as in other cases, it was related to undisclosed extracts, adulterants, heavy metals, bacterial contaminants and chemical toxins. In this report, we describe a new weight loss supplement, Safe Lean™, associated with anicteric acute hepatitis in a young obese woman. We discuss potential toxicity of disclosed components of the weight loss supplement, provide an in-depth analysis on the chemical and toxicology of the offending product and discuss discrepancies in identifying good manufacturing and labelling practices associated with this product.

CASE REPORT

A previously healthy 33-year-old woman complained of nausea, loss of appetite and general well-being for one week. The patient reported using a multi-ingredient, non-stimulant weight loss health supplement called Safe Lean™ (Figure 1; marketed by Signorah Healthcare Ltd, Chennai, India; manufactured by Medsys Biotech, Sirmour, Himachal Pradesh). Safe Lean™ contains *Garcinia cambogia* (Malabar tamarind, 600 mg), *Allium sativum* (garlic, 250 mg) and *Trigonella foenum graecum* (fenugreek, 100 mg). She took one capsule twice daily before meals as recommended for one month before onset of symptoms. She did not consume alcohol or abuse oral and injectable recreational drugs. Her other medications included calcium and vitamin D supplements and folic acid (5 mg) once daily, in the last three months. On evaluation, there was no stigmata of chronic liver disease. Blood work revealed a total serum bilirubin level 2.8 (upper limit of normal, ULN 1.1 mg/dL), direct bilirubin 1.7 (ULN 0.2 mg/dL), aspartate aminotransferase 886 (ULN 36 U/L), alanine aminotransferase 960 (ULN 45 U/L), alkaline phosphatase 148 (ULN 120 U/L), gamma-glutamyl transferase level 125 (ULN 35 U/L), albumin 4.2 (ULN 5.5 g/dL) and international normalized ratio 1.7 (normal < 1.2).

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Abbreviations: DMAA: Dimethylamylamine; DNA: Deoxyribonucleic Acid; GMP: Good Manufacturing Practices; HDS: Herbal Dietary Supplements; ICP-OES: Inductively Coupled Plasma – Optical Emission Spectrometry; RUCAM: Roussel Uclaf Causality Assessment Method; TQ-GC-MS-MS: Triple Quadruple Gas Chromatography and Dual Mass Spectroscopy; ULN: Upper Limit of Normal; WHO: World Health Organization

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Figure 1 Retrieved samples of Safe Lean™ dietary and herbal supplement that caused acute hepatitis in the patient.

Etiological workup was negative for viral serology (hepatitis A and E virus immunoglobulin M, hepatitis B virus surface antigen and core antibody, hepatitis C virus antibody, cytomegalovirus DNA, Epstein–Barr virus immunoglobulin M, Herpes and Zoster virus immunoglobulin M); negative syphilis rapid plasma regain; negative autoimmune markers (antinuclear antibody, anti-liver kidney muscle antibody type 1, anti-smooth muscle antibody and anti-mitochondrial antibody with normal serum gamma globulins). Renal function tests and complete blood counts were within normal range. She had normal levels of ceruloplasmin and ferritin. A computed tomography scan of the abdomen showed hepatomegaly. In the absence of known causes of liver diseases, drug induced liver injury, secondary to Safe Lean™ was considered, with Roussel Uclaf Causality Assessment Method (RUCAM) score 8 (probable adverse drug reaction, Supplementary Table 1).

The patient was advised to stop the offending drug and was put on a normal diet, and oral N-acetyl cysteine for a week. After a week, her liver enzymes decreased to >50% from the elevated levels and at four weeks, they completely normalized. A rechallenge with Safe Lean™ for confirmation was offered, but the patient denied. At two-month follow up, her liver tests remained within normal limits. We retrieved the Safe Lean™ samples from the patient and subjected it to chemical analysis and toxicology. Heavy metals testing was done using inductively coupled plasma – optical emission spectrometry (ICP-OES, Agilent Technologies, Santa Clara, CA, USA) and volatile organic compounds, chemical adulterants, pesticides and insecticide contamination were screened using triple quadruple gas chromatography and dual mass spectroscopy (TQ-GC-MS-MS, Thermo Fisher Scientific, Waltham, MA, USA). We found high levels of thallium, cadmium, chromium, vanadium, barium and lead (Table 1) and traces of ethylhydrazine in Safe Lean™ supplements.

Table 1 Heavy Metal Component Estimation in the Weight Loss Supplement Safe Lean™.

Metals	Quantification (mg/kg)
Arsenic	Below detection limits
Cadmium	16.64
Barium	7.73
Chromium	2.84
Cobalt	0.20
Beryllium	Below detection limits
Lead	1.57
Vanadium	1.86
Thallium	4.21
Mercury	Below detection limits

DISCUSSION

Garcinia cambogia is rich in hydroxy-citric acid and is widely promoted for weight loss and previously shown to cause episodes of acute liver injury and acute liver failure (in patients taking Hydroxycut™). Corey et al. reported on a middle-aged woman who took 1000 mg/day of *G. cambogia* for 15 days leading to liver failure necessitating liver transplantation.[3] A 42-year-old female after taking pure *G. cambogia* for one week developed severe liver test abnormalities and coagulation failure recovering after the offending agent was withdrawn.[4] A systematic review and meta-analysis of randomized clinical trials concluded that Garcinia extracts caused short-term weight loss, but the magnitude of the effect was small, and the clinical relevance uncertain.[5] None of the components detected in Safe Lean™ were disclosed on the packaging and a product insert was lacking as well. Chromium (recommended daily intake 50 μg/day in adults) related acute hepatitis, thrombocytopenia, and renal failure has been described in literature.[6] Higher cadmium exposures have been shown to be associated with severe steatohepatitis in men, and hepatic necroinflammation in women. Patients with higher creatinine-corrected urinary cadmium had over a threefold increased risk of liver disease mortality unrelated to cancer of the liver.[7,8] Chloride salts of barium have been implicated in severe liver disease leading to liver failure.[9,10] Thallium, a cumulative poison, as per the International Programme on Chemical Safety, has been associated with necroinflammation and severe steatosis of the liver in case reports and small series.[11,12] In vivo and in vitro data demonstrate sodium metavanadate induced liver injury to be related to the metal disruptive effect on the mitochondrial respiratory complexes. However, human studies are lacking.[13,14]

In our patient, the exposure to heavy metals was higher than recommended safe levels. Taking into consideration the multiple components in Safe Lean™, both disclosed and undisclosed, we believe that complex interactions led

to severe hepatitis in our patient. This would have been exacerbated in the presence of additional chemical constituents such as hydrazine derivatives (shown to cause fatty liver, hepatocellular necrosis and potentiates carcinogenesis in the long term) during manufacturing that may not have followed Good Manufacturing Practice (GMP) as recommended by current drug regulatory laws.[15] We looked into the company website (http://www.signorah.com/) for details, descriptions, complete component disclosures, preclinical, clinical and post mar keting surveillance data on safety and efficacy of Safe Lean™ and found none. The manufacturer's page (http://www.medisysbiotech.com) did not listSafe Lean™ as one their herbal products.

CONCLUSION

In patients with acute hepatitis with unknown aetiology, a strong clinical insight into food and supplemental drug intake must be sought. Use of weight loss supplements and herbal dietary products might seem trivial and safe to the patient but could emerge as the culprit in promoting or causing liver injury in many instances. Surveillance for untested, spurious and misbranded proprietary herbal and dietary supplements is an unmet need and require extensive public and private partnerships for identification and regulation.

CONFLICTS OF INTEREST

The authors have none to declare.

APPENDIX A SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jceh.2018.05.001.

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