Published in final edited form as:

Clin Liver Dis. 2017 February ; 21(1): 135–149. doi:10.1016/j.cld.2016.08.010.

Herbal and Dietary Supplement Induced Liver Injury

Ynto S. de Boer^{1,2} and Averell H. Sherker³

¹Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD ²Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands ³Liver Diseases Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Summary

The increase in the use of herbal and dietary supplements (HDS) over the last decades has been accompanied with an increase in the reports of HDS associated hepatotoxicity. The spectrum of HDS induced liver injury is diverse and the outcome may vary from transient liver test elevations to fulminant hepatic failure resulting in death or requiring liver transplantation. There are no validated standardized tools to establish the diagnosis, but some HDS products do have a typical clinical signature that may help to identify HDS induced liver injury.

Keywords

Herbals; Dietary supplements; Liver; Toxicity; Drug-induced liver injury

Introduction

Epidemiology

Herbs and botanicals, as well as their metabolites, constituents and extracts, are included in the definition of “dietary supplements” in United States Federal law.(1) The term “Herbal and Dietary Supplements” (HDS) is redundant but commonly used to categorize these products. Although regulated by the Food and Drug Administration, dietary supplements are not subject to the safety monitoring and approval process of pharmaceutical drugs.

Despite the facts that these agents generally lack proof of efficacy and that their manufacturers are not permitted to make medical claims, these products have gained

Correspondence to: Averell H. Sherker, MD, FRCPC, FAASLD, DDDN, NIDDK, NIH, 6011 Executive Blvd, Room 6003, Bethesda, MD 20852, Telephone: + 1 301 451 6207, Fax: +1 301 480 8300, averell.sherker@nih.gov; **Additional Author Contact:** Ynto S. de Boer, MD, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands, Telephone: +31 20 444 4444, ynto.deboer@nih.gov, y.deboer@vumc.nl.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors have nothing to disclose.

extremely wide acceptance and their use has increased over recent decades. During this time, the estimated number of supplements marketed in the United States has increased over ten-fold -- from ~4000 in 1993 to ~55000 in 2012.(2, 3) About half of the adult population in the United States reports having used at least one dietary supplement in the past month.(4, 5) These products are more commonly used by non-Hispanic whites, at older age and with higher levels of education.(6-9) The majority of alternative medicine users feel that the use of HDS products is consistent with their attitudes towards health and life, and that these agents contribute to their wellbeing.(10) The use of HDS is associated with considerable expense. In 2007, \$14.8 billion was spent out of pocket on herbal or complementary nutritional products, equivalent to one-third of the out-of-pocket expenditures associated with prescription drug use in the United States.(11)

Nationally, it is estimated that 23,000 emergency department visits each year can be attributed to adverse effects associated with the use of HDS.(12) While there have been well-documented outbreaks of acute liver injury associated with specific dietary supplements, the true incidence of HDS-induced liver injury (HILI) is difficult to estimate. In Spain, 2% of investigated cases of drug-induced liver injury have been attributed to HDS(13), while in Iceland the number is approximately 16%.(14) The NIH-funded Drug-Induced Liver Injury Network (DILIN) has recently reported that, of total DILI cases adjudicated between 2004 and 2013, attribution to HDS has increased from 7% to 20% (Figure 1).(15) Among patients presenting with acute liver failure, those whose disease was attributed to HDS use are more likely to undergo liver transplantation than those associated with prescription medicines (56.1 vs. 31.9%, $P < 0.005$). (16)

Regulation and quality control

In the United States, manufacturers of dietary supplements containing ingredients that were introduced after October 15, 1994, are required to notify the FDA before marketing and to provide a rationale for the safety of the ingredients, such as historical use.(1) Safety testing or FDA approval of dietary supplements is not required before marketing. Only in case of serious adverse events (hospitalization or death) is post marketing notification of the FDA required.(17) Recent examples of HDS products that were withdrawn from the market include OxyElite Pro in 2013 (caused acute liver failure)(18) and Hydroxycut (hepatocellular injury with jaundice).(19) In the European Union (EU), herbal and dietary supplements are regulated under the Traditional Herbs Medicine Products Directive 2004/24/EC.(20, 21) This directive stipulates that if a product has been shown to be safely used over an acceptable long period (over 30 years with 15 years use within the EU), it may be registered through a simplified procedure if the product is not administered parenterally and does not require a medical prescription. In contrast to U.S. regulations, in Europe food supplements such as vitamin and mineral substances are regulated by the European Food Safety Authority (AFSA) according to Directive 2002/46/EC,(22) whereas herbal medical products are overseen by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA).(23) To further complicate the regulatory landscape, many HDS products are acquired online through the internet, where vendors and manufacturers may not be easily identifiable and enforcement is extremely difficult (Tables 1 and 2).

Clinical presentation and Diagnosis

HDS induced liver injury may manifest virtually the entire spectrum of acute and chronic liver disease. In epidemic outbreaks (e.g., Oxyelite Pro) affected individuals may present with a relatively consistent phenotype.(24) A small number of agents (e.g., anabolic steroids) have an idiosyncratic clinical presentation which may trigger a high index of suspicion, even in the absence of a disclosed history of exposure. More typically, sporadic cases present with hepatocellular, cholestatic or mixed pattern of liver injury with varying degrees of severity and hepatic dysfunction. Patients may present with asymptomatic liver enzyme elevations, nonspecific constitutional symptoms, symptoms typical of acute hepatitis (icterus, nausea, fatigue, right upper quadrant abdominal pain) or acute liver failure with hepatic encephalopathy. These cases may have an autoimmune phenotype, as the presence of autoantibodies was reported to be 29% in one series of patients with HDS induced liver injury.(25) Other causes for liver injury such as biliary obstruction (cholelithiasis and malignancy), viral hepatitis (hepatitis A, B, C, E, CMV and EBV), alcoholic and nonalcoholic steatohepatitis, autoimmune liver disease (autoimmune hepatitis [AIH], primary sclerosing cholangitis [PSC] and primary biliary cholangitis [PBC]), hemochromatosis and Wilson disease should be considered and excluded. Unlike prescription drugs, HDS are often perceived as ‘natural’ (and, by extension, harmless) products by patients and may not be considered relevant to disclose. Individuals who have been using a product for an extended period of time may legitimately discount its role in their acute illness, not recognizing that formulations may change without notice, sourcing of ingredients may vary, and that unregulated quality control processes may lead to significant lot-to-lot variations. Patients may be reluctant or embarrassed to share their use of alternative therapeutics with conventional medical practitioners and in some cases (e.g., anabolic steroids), consumers will deny use, knowing that the practice is illegal. Patients with liver disease should be questioned directly about their use of prescription medications, over-the-counter products, and HDS. If the diagnosis remains uncertain or the index of suspicion is high, the patient should be questioned about HDS use again. It may be helpful to ask the patient or a family member to bring all of their medications and supplements to the clinic or hospital. Figure 2 is a rolling suitcase full of HDS products brought to clinic (and being consumed) by a patient with marked jaundice and advanced subacute liver disease who repeatedly denied HDS use until told of her physician’s suspicion after she underwent liver biopsy. Figure 3 shows the pharmacopeia of HDS being used by a patient with liver injury, illustrating the challenges of ascribing causality to a specific agent. Even when there is a high degree of suspicion for HILI, it may be difficult to establish a diagnosis with a high degree of certainty. To address this issue, Naranjo et al. (1981) developed an Adverse Drug Reaction Probability Scale (ADRPS) to establish the probability of an adverse drug reaction, primarily in controlled-trials and studies.(26) The score is derived from 10 simple questions that can add up to a total score that ranges from –4 to 14.(26) Although widely used, this system was shown to have a limited applicability in estimating liver injury due to drugs.(27) Instead, they found that the Roussel Uclaf Causality Assessment Method (RUCAM), performed better (See Al Sehu, Xiaochao Ma, and R Venkataramanan’s article “Mechanisms of drug induced hepatotoxicity,” in this issue).(27-30)

Pattern of injury

As with ‘classical’ DILI, patients with liver injury due to HDS can be classified into hepatocellular, mixed or cholestatic liver injury. This pattern is defined by the R value ($[ALT/ULN] \div [Alk P/ULN]$), in which a value >5 is interpreted as hepatocellular, <2 as cholestatic and 2-5 as mixed hepatic injury. Across the world, HILI appears to be more commonly associated with an hepatocellular pattern of injury than prescription DILI.(14, 25, 31-35) In DILI, hepatocellular injury with jaundice has been described to have a more severe outcome than is seen in mixed or cholestatic patterns of injury (Hy’s Law).

Unique aspects of HDS induced liver injury

The mechanisms through which HDS products cause hepatotoxicity are variable and specific to the substance consumed. In HILI, it is important to note that substances may be safe in their ‘natural’ form but highly concentrated preparations and synthesized chemicals, although marketed as natural, may be associated with toxicities (e.g., catechins found in green tea preparations and synthetic aegeline in OxyELITE Pro(36)). A major challenge in evaluating liver injury due to HDS products is the inaccuracies with respect to product labeling. Contrary to regulations, some products do not display a label listing ingredients. In the DILIN experience, it was found that 29 of 73 HDS products (40%) taken for various purposes (body building, weight loss, immune support and others) and causing liver injury, did not identify green tea extract (GTE) or any of its component catechins on the label despite containing catechins by analytic chemical methods.(37) Interestingly, 3 of 18 (17%) investigated products that did list catechins or GTE on the label did not contain these substances in detectable concentrations. In general, label-reported concentrations of GTE did not accurately reflect the actual contents.

Adulteration of HDS products has been described. Tablets of the Chinese herbal product Jin Bu Huan Anodyne listed *Polygala chinensis* as its single effective ingredient, but were found to contain levo-tetrahydropalmatine, which is found in the plant genera *Stephania* and *Corydalis* but not in the genus *Polygala*.(38) This product was responsible for an outbreak of severe hepatotoxicity before it was removed from the market.

Given the lack of regulatory oversight on production and manufacturing, there is a potential for contamination of HDS product. A report on the hepatotoxicity associated with Herbalife products identified bacterial contamination with *Bacillus subtilis* as a potential cause for the products’ hepatotoxicity profile(39).

Hepatotoxicity associated with specific HDS

Anabolics

Marketed anabolic steroids are generally synthetic chemicals and are not HDS as strictly defined.(1) However, they are typically included in the discussion of HILI. Liver injury due to ingestion of anabolic steroids/bodybuilding compounds has a very typical clinical presentation. It mostly involves young men involved in bodybuilding, weight training, or athletics who, despite modest liver enzyme elevations, present with marked jaundice and pruritus.(15, 40) It typically has a relatively mild course and completely resolves, albeit

often slowly, after the cessation of the product. Pruritus may be debilitating. The use of anabolic steroids or enhancing products is often emphatically denied by the patient, yet the diagnosis can be made confidently based on the presentation and clinical course. Frequently, the patient does not return for a scheduled follow-up visit when feeling better (“Jay’s Law”^a). Patients should be warned that the use of these agents may be illegal.

Black cohosh

Black cohosh (*Cimicifuga/Actaea racemosa*) is an herbal extract that was traditionally used by Native Americans to treat a wide variety of symptoms, including joint aches, myalgia and gynecologic symptoms. Today it is primarily used for the treatment of post-menopausal symptoms. The mechanism of action is unknown, but there have been reports on hepatotoxicity with and without autoimmune features,(41-43) which has led to the publication of a cautionary statement by the US Dietary Supplement Information Expert Committee.(44) However, a more recent meta-analysis of five randomized, double-blind, controlled clinical trials found no evidence that isopropanolic extracts of black cohosh have any adverse effect on liver function.(45) Black cohosh has been known to be adulterated with other species of *Actaea* (*Actaea pachypoda* Ell. (white cohosh) and *Actaea podocarpa* DC. (yellow cohosh) from China which may be responsible for the hepatotoxicity reported.(46)

Germander

The blossoms of wall germander (*Teucrium chamaedrys*) have long been used in folk medicine in the Middle East and Mediterranean region as treatment for dyspepsia, obesity, diabetes and abdominal colic. Despite its wide use, it was found in the early 1990s that herbal preparations, in the form of tea or capsules, could cause significant liver injury. The injury is characterized by an hepatocellular pattern associated with marked jaundice, in the absence of immunoallergic or autoimmune features.(47) The latency to onset of injury is relatively short, usually within 30 days of starting the preparation. Although fatal cases and liver transplantation have been reported, the injury generally resolves after the cessation of the agent.(48) Re-exposure to germander leads to rapid recurrence of the injury.(47) The toxicity is thought to arise due to CYP3A4 activation of the component furan ring Teucrin A, which can then alkylate intracellular epoxide hydrolase, leading to formation of anti-microsomal epoxide hydrolase autoantibodies(49). It has been hypothesized that the anorexogenic properties of germander may actually relate to a mild hepatitis.

Green tea

Green tea (*Camellia sinensis*) contains polyphenols known as catechins (+-catechin, gallic catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate). An intake of 2-3 cups of green tea per day will not generally lead to hepatotoxicity. However, HDS products such as SlimQuick, generally intended for weight loss may contain higher doses of GTE, which can induce hepatotoxicity.(50-53) Epigallocatechin gallate (EGCG) is the most abundant green tea polyphenol, and is believed to be the most active and

^aObservation made by Dr. Jay H. Hoofnagle in DILIN Causality Assessment, 2013.

potent hepatotoxic component.(50) Genomic investigation in outbred mice identified genes that were associated with EGCG toxicity. There is a suggestion that analogous human genetic variants may be associated with susceptibility to GTE hepatotoxicity.(54)

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids are found in a large number of plants, including several used as HDS. Among these are *Senecio*, and *Symphytum* (Comfrey) species. Sinusoidal obstruction syndrome (SOS, previously known as hepatic veno-occlusive disease) was first described in 1954 among Jamaicans drinking “bush teas” brewed from *Senecio*.(55) Reports from South Africa(56) (*Senecio*-contaminated bread), India (57) (*Crotalaria*-contaminated cereal), Afghanistan(58) (*Heliotropium*-contaminated wheat) and the southwestern United States(59-61) (Comfrey used as HDS) have implicated pyrrolizidine alkaloids in SOS. Many reports describe the disease in children suggesting either an increased susceptibility or a dose effect.(62) Interestingly, the pulmonary vascular bed is also sensitive to the effects of pyrrolizidine alkaloids.(63) Sinusoidal obstruction syndrome may present as an acute, subacute or chronic liver injury characterized by weight gain, ascites and tender hepatomegaly. Hepatic sinusoidal cells appear to be the primary target of pyrrolizidine alkaloids. These cells are damaged and swell, impeding sinusoidal blood flow, inducing hemorrhage, and ultimately resulting in sinusoidal obstruction.(64)

Kava kava

Kava kava (*Piper methysticum*) is used to treat anxiety and depressive disorders. However, numerous worldwide reports of fulminant hepatotoxicity, both hepatocellular and cholestatic, have led to the withdrawal of distribution licenses in the US, Europe and Australia.(65-67) Both immunoallergic and idiosyncratic factors (including CYP2D6 deficiency), have been implicated. (65, 66)

Traditional Chinese Medicine

In the art of Traditional Chinese Medicine (TCM), specific herbs are selected in different preparations for their supposed properties to treat disease within the human body. TCMs have been used to treat conditions such as viral hepatitis for centuries. In China, currently, approximately 40% of cases of DILI are attributed to the use of TCMs, and have been responsible for cases of acute liver failure with associated coagulopathy.(68, 69)

Proprietary mixes

Herbalife

In 2004, a report by Elinav et al. implicated ingestion of Herbalife products in 12 patients who developed DILI, manifest as acute fulminant hepatitis.(70) Herbalife products consist of a wide range of different mixtures, usually being taken for the purpose of weight loss or general well-being. Identified ingredients include *Solidago gigantea*, *Ilex paraguariensis*, *Petroselinum crispum*, *Garcinia cambogia*, *Spiraea*, *Matricaria chamomilla*, *Liquiritia*, *Foeniculum amare*, *Humulus lupulus*, *Chromium* and numerous others. Additionally, the proprietary formula of these products, contain a wide range of listed and unlisted ingredients, which makes it challenging to identify a single responsible component with any

degree of certainty.(71) In the initial cohort of cases implicated, the injury resolved spontaneously in 11 of 12 (92%) patients; one patient with preexisting chronic hepatitis B died after undergoing liver transplantation. Three patients developed recurrent liver test abnormalities after resuming ingestion of Herbalife products. Since then, several reports have shown similar associations of HILI with Herbalife products, also suggesting contamination with *Bacillus subtilis* as a potential cause for its hepatotoxicity profile.(39, 72) Employees of Herbalife have aggressively criticized reports of Herbalife-associated hepatotoxicity (73, 74), but their criticisms have been effectively rebutted.(75)

OxyELITE Pro

Between February 2012 and February 2014 the FDA received 55 reports of liver disease in consumers of OxyELITE Pro. The typical clinical course consisted of a severe acute hepatitis pattern of injury with a median time to onset of 60 days. Hospitalization was required in 33 (60%) cases and liver transplantation in 3 (5%).(76) In early 2013 the formula of OxyELITE Pro had been changed, substituting 1,3-Dimethylamylamine, which had been associated with cardiovascular toxicity, with aegeline.(76) Early reports of liver injury were from Hawaii, where an initial cluster of 7 patients was reported to develop liver injury in the period between May and September 2013.(24, 77) Following this report, other cases were identified in an outbreak investigation performed by the Hawaii Department of Health, Centers for Disease Control and Prevention (CDC) and FDA.(77) The product was recalled and the manufacturer was required to discontinue the distribution of OxyELITE Pro.(18) Aegeline, derived from the bark of the Bael tree in India, has long been used as a traditional remedy but the component implicated in the OxyELITE Pro outbreak was synthetic.(36)

Hydroxycut

Hydroxycut products are generally marketed and used as a weight loss supplements. Two published case series implicated the use of some Hydroxycut products to the occurrence of liver injury, presenting predominantly with an hepatocellular pattern of injury and symptoms of jaundice, fatigue, nausea, vomiting, and abdominal pain.(78, 79) Several Hydroxycut products were voluntarily recalled in 2009, following a published FDA warning related to the use of Hydroxycut.(19)

Move Free Advanced

Move Free Advanced is a widely distributed dietary supplement, sold over the counter in the United States for treatment of sore joints and to improve flexibility and mobility. The product contains glucosamine, chondroitin, hyaluronic acid, and proprietary Uniflex consisting of Chinese skullcap (*Scutellaria baicalensis*) and black catechu. In a 2010 report, the ingestion of Move Free was identified as a probable cause for the development of cholestatic hepatitis which resolved after discontinuation of the supplement.(80) In one patient, Move Free was not initially recognized as the agent responsible for the injury and the patient restarted the supplement, after which liver injury recurred. A liver biopsy performed at that time was consistent with acute drug induced liver injury.(81) In one patient, pulmonary infiltrates developed simultaneous with the hepatotoxicity and resolved completely with cessation of the supplement.(82) Diterpenoid compounds in *Scutellaria*

baicalensis, have previously been shown to cause apoptosis in isolated rat hepatocytes, through reactive metabolites formed by CYP3A.(83)

Conclusion/summary

The increase in the use of herbal and dietary supplements (HDS) and a growing awareness of the potential for these agent to cause liver injury has been associated with an increase in reports of HDS associated hepatotoxicity. Limited regulatory oversight, inaccurate product labeling, adulterants and inconsistent sourcing of constituent ingredients may all contribute to the potential for toxicity. The spectrum of HDS induced liver injury is diverse and the outcome may vary from transient liver test abnormalities to acute hepatic failure requiring liver transplantation, or resulting in death. The most commonly implicated products include bodybuilding and weight loss products. There are no validated standardized tools to establish the diagnosis, but some HDS products do have a clear clinical signature that can make diagnosis almost certain. The keys to diagnosis are a high level of suspicion and a comprehensive workup to eliminate competing etiologies. Management is generally supportive and nonspecific.

References

1. Dietary Supplement Health and Education Act of 1994. 1994. Public Law 103-417, 108 Stat 4325
2. Report of the Commission on Dietary Supplement Labels. Department of Health and Human Services, Office of Disease Prevention and Health Promotion; Washington, DC: 1997.
3. Dietary supplements: FDA may have opportunities to expand its use of reported health problems to oversee products (GAO-13-244). Government Accountability Office; Washington, DC: Mar 13. 2013 Report No
4. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, et al. Dietary supplement use in the United States, 2003-2006. *J Nutr*. 2011; 141(2):261–6. Epub 2010/12/24. [PubMed: 21178089]
5. Picciano MF, Dwyer JT, Radimer KL, Wilson DH, Fisher KD, Thomas PR, et al. Dietary supplement use among infants, children, and adolescents in the United States, 1999-2002. *Arch Pediatr Adolesc Med*. 2007; 161(10):978–85. Epub 2007/10/03. [PubMed: 17909142]
6. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol*. 2004; 160(4):339–49. Epub 2004/08/03. [PubMed: 15286019]
7. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med*. 2013; 173(5):355–61. Epub 2013/02/06. [PubMed: 23381623]
8. Foote JA, Murphy SP, Wilkens LR, Hankin JH, Henderson BE, Kolonel LN. Factors associated with dietary supplement use among healthy adults of five ethnicities: the Multiethnic Cohort Study. *Am J Epidemiol*. 2003; 157(10):888–97. Epub 2003/05/15. [PubMed: 12746241]
9. Block G, Jensen CD, Norkus EP, Dalvi TB, Wong LG, McManus JF, et al. Usage patterns, health, and nutritional status of long-term multiple dietary supplement users: a cross-sectional study. *Nutr J*. 2007; 6:30. Epub 2007/10/26. [PubMed: 17958896]
10. Astin JA. Why patients use alternative medicine: results of a national study. *JAMA*. 1998; 279(19):1548–53. Epub 1998/05/30. [PubMed: 9605899]
11. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. *Natl Health Stat Report*. 2009; (18):1–14. Epub 2009/09/24.
12. Geller AI, Shehab N, Weidle NJ, Lovegrove MC, Wolpert BJ, Timbo BB, et al. Emergency Department Visits for Adverse Events Related to Dietary Supplements. *N Engl J Med*. 2015; 373(16):1531–40. Epub 2015/10/16. [PubMed: 26465986]

13. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005; 129(2):512–21. Epub 2005/08/09. [PubMed: 16083708]
14. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013; 144(7):1419–25. 25 e1–3. quiz e19–20. Epub 2013/02/20. [PubMed: 23419359]
15. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology*. 2014; 60(4):1399–408. Epub 2014/07/22. [PubMed: 25043597]
16. Hillman L, Gottfried M, Whitsett M, Rakela J, Schilsky M, Lee WM, et al. Clinical Features and Outcomes of Complementary and Alternative Medicine Induced Acute Liver Failure and Injury. *Am J Gastroenterol*. 2016 Epub 2016/04/06.
17. Dietary Supplement and Nonprescription Drug Consumer Protection Act. 2006. Public Law 109-462, 120 Stat 4500, Pub. L. No. 109-462 Stat. 4500
18. U.S. Food and Drug Administration. FDA investigates acute hepatitis illnesses potentially linked to products labeled OxyElite Pro. Jul 30. 2014 Report No
19. U.S. Food and Drug Administration Recall - Firm Press Release Iovate Health Sciences U.S.A., Inc. Voluntarily Recalls Hydroxycut-Branded Products. May 1. 2009 Report No
20. European Commission. Herbal Medicinal Products. Mar 31. 2004 Report No
21. Directive 2004/24/EC Of The European Parliament And Of The Council. 2004.
22. Directive 2002/46/EC of The European Parliament And Of The Council. 2002.
23. European Medicines Agency. Committee on Herbal Medicinal Products (HMPC). 2004.
24. Roytman MM, Porzgen P, Lee CL, Huddleston L, Kuo TT, Bryant-Greenwood P, et al. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. *Am J Gastroenterol*. 2014; 109(8):1296–8. Epub 2014/08/06. [PubMed: 25091255]
25. Bessone F, Hernandez N, Sanchez A, di Pace M, Arrese M, Brahm JR, et al. The Spanish-Latin American DILI Network: preliminary results from a collaborative strategie initiative. *J Hepatol*. 2013; 58(Suppl 1):212–3. [PubMed: 23022497]
26. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30(2):239–45. Epub 1981/08/01. [PubMed: 7249508]
27. Garcia-Cortes M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther*. 2008; 27(9):780–9. Epub 2008/02/21. [PubMed: 18284654]
28. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990; 11(2):272–6. Epub 1990/09/01. [PubMed: 2254635]
29. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993; 46(11):1323–30. Epub 1993/11/01. [PubMed: 8229110]
30. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs--II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993; 46(11):1331–6. Epub 1993/11/01. [PubMed: 8229111]
31. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008; 135(6):1924–34. 34 e1–4. Epub 2008/10/29. [PubMed: 18955056]
32. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology*. 2010; 52(6):2065–76. Epub 2010/10/16. [PubMed: 20949552]
33. Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug-induced liver injury at an Asian center: a prospective study. *Liver Int*. 2007; 27(4):465–74. Epub 2007/04/04. [PubMed: 17403186]
34. Suk KT, Kim DJ, Kim CH, Park SH, Yoon JH, Kim YS, et al. A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol*. 2012; 107(9):1380–7. Epub 2012/06/27. [PubMed: 22733303]

35. Medina-Cáliz I, González-Jiménez A, Bessone F, Hernández N, Sánchez A, Di Pace M, et al. Variations in drug-induced liver injury (DILI) between different prospective dili registries. *Clinical Therapeutics*. 2013; 35(8):e24.
36. FDA Uses New Authorities To Get OxyElite Pro Off the Market. 2013.
37. Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. *Dig Dis Sci*. 2013; 58(9):2682–90. Epub 2013/04/30. [PubMed: 23625293]
38. Woolf GM, Petrovic LM, Rojter SE, Wainwright S, Villamil FG, Katkov WN, et al. Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med*. 1994; 121(10):729–35. Epub 1994/11/15. [PubMed: 7944049]
39. Stickel F, Droz S, Patsenker E, Bogli-Stubler K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with *Bacillus subtilis*. *J Hepatol*. 2009; 50(1):111–7. Epub 2008/11/18. [PubMed: 19010564]
40. Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, Stephens C, Garcia-Cortes M, Garcia-Munoz B, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. *Aliment Pharmacol Ther*. 2015; 41(1):116–25. Epub 2014/11/15. [PubMed: 25394890]
41. Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl*. 2006; 12(6):989–92. Epub 2006/05/25. [PubMed: 16721764]
42. van de Meerendonk HW, van Hunsel FP, van der Wiel HE. Autoimmune hepatitis induced by *Actaea racemosa*. Side effects of an herb extract. *Ned Tijdschr Geneesk*. 2009; 153(6):246–9. Epub 2009/03/11. Auto-immuunhepatitis door zilverkaars. Bijwerking van een kruidenextract. [PubMed: 19271447]
43. Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. *Menopause*. 2004; 11(5):575–7. Epub 2004/09/10. [PubMed: 15356412]
44. Mahady GB, Low Dog T, Barrett ML, Chavez ML, Gardiner P, Ko R, et al. United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause*. 2008; 15(4 Pt 1):628–38. Epub 2008/03/15. [PubMed: 18340277]
45. Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. *Menopause*. 2011; 18(4):366–75. Epub 2011/01/14. [PubMed: 21228727]
46. Verbitski SM, Gourdin GT, Ikenouye LM, McChesney JD, Hildreth J. Detection of *Actaea racemosa* adulteration by thin-layer chromatography and combined thin-layer chromatography-bioluminescence. *J AOAC Int*. 2008; 91(2):268–75. Epub 2008/05/15. [PubMed: 18476337]
47. Larrey D, Vial T, Pauwels A, Castot A, Biour M, David M, et al. Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. *Ann Intern Med*. 1992; 117(2):129–32. Epub 1992/07/15. [PubMed: 1605427]
48. Dag MS, Aydinli M, Ozturk ZA, Turkbeyler IH, Koruk I, Savas MC, et al. Drug- and herb-induced liver injury: a case series from a single center. *Turk J Gastroenterol*. 2014; 25(1):41–5. Epub 2014/06/12. [PubMed: 24918129]
49. De Berardinis V, Moulis C, Maurice M, Beaune P, Pessayre D, Pompon D, et al. Human microsomal epoxide hydrolase is the target of germander-induced autoantibodies on the surface of human hepatocytes. *Mol Pharmacol*. 2000; 58(3):542–51. Epub 2000/08/23. [PubMed: 10953047]
50. Lambert JD, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (–)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol*. 2010; 48(1):409–16. Epub 2009/11/04. [PubMed: 19883714]
51. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann Intern Med*. 2006; 144(1):68–71. Epub 2006/01/04. [PubMed: 16389263]
52. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol*. 2009; 65(4):331–41. Epub 2009/02/10. [PubMed: 19198822]

53. Weinstein DH, Twaddell WS, Raufman JP, Philosophie B, Mindikoglu AL. SlimQuick - associated hepatotoxicity in a woman with alpha-1 antitrypsin heterozygosity. *World J Hepatol.* 2012; 4(4): 154–7. Epub 2012/05/09. [PubMed: 22567188]
54. Church RJ, Gatti DM, Urban TJ, Long N, Yang X, Shi Q, et al. Sensitivity to hepatotoxicity due to epigallocatechin gallate is affected by genetic background in diversity outbred mice. *Food Chem Toxicol.* 2015; 76:19–26. Epub 2014/12/03. [PubMed: 25446466]
55. Bras G, Jelliffe DB, Stuart KL. Veno-occlusive disease of liver with nonportal type of cirrhosis, occurring in Jamaica. *AMA Arch Pathol.* 1954; 57(4):285–300. Epub 1954/04/01. [PubMed: 13147641]
56. Wilmot FC, Robertson GW. Senecio disease or cirrhosis of the liver due to Senecio poisoning. *Lancet.* 1920; (2):848–9.
57. Tandon RK, Tandon BN, Tandon HD, Bhatia ML, Bhargava S, Lal P, et al. Study of an epidemic of venoocclusive disease in India. *Gut.* 1976; 17(11):849–55. Epub 1976/11/01. [PubMed: 1001974]
58. Mohabbat O, Younos MS, Merzad AA, Srivastava RN, Sediq GG, Aram GN. An outbreak of hepatic veno-occlusive disease in north-western Afghanistan. *Lancet.* 1976; 2(7980):269–71. Epub 1976/08/07. [PubMed: 59848]
59. Stillman AS, Huxtable R, Consroe P, Kohnen P, Smith S. Hepatic veno-occlusive disease due to pyrrolizidine (Senecio) poisoning in Arizona. *Gastroenterology.* 1977; 73(2):349–52. Epub 1977/08/01. [PubMed: 873137]
60. Bach N, Thung SN, Schaffner F. Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med.* 1989; 87(1):97–9. Epub 1989/07/01. [PubMed: 2741990]
61. Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venoocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology.* 1985; 88(4):1050–4. Epub 1985/04/01. [PubMed: 3972224]
62. Steenkamp V, Stewart MJ, Zuckerman M. Clinical and analytical aspects of pyrrolizidine poisoning caused by South African traditional medicines. *Ther Drug Monit.* 2000; 22(3):302–6. Epub 2000/06/13. [PubMed: 10850397]
63. Shubat PJ, Banner W Jr. Huxtable RJ. Pulmonary vascular responses induced by the pyrrolizidine alkaloid, monocrotaline, in rats. *Toxicol.* 1987; 25(9):995–1002. Epub 1987/01/01. [PubMed: 3124302]
64. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis.* 2002; 22(1):27–42. Epub 2002/04/03. [PubMed: 11928077]
65. Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. *Ann. Intern Med.* 2001; 135(1):68–9. Epub 2001/07/04.
66. Stickel F, Baumuller HM, Seitz K, Vasilakis D, Seitz G, Seitz HK, et al. Hepatitis induced by Kava (*Piper methysticum* rhizoma). *J Hepatol.* 2003; 39(1):62–7. Epub 2003/06/25. [PubMed: 12821045]
67. From the Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products--United States, Germany, and Switzerland, 1999-2002. *JAMA.* 2003; 289(1):36–7. Epub 2003/01/08. [PubMed: 12515265]
68. Zhao P, Wang C, Liu W, Chen G, Liu X, Wang X, et al. Causes and outcomes of acute liver failure in China. *PLoS One.* 2013; 8(11):e80991. Epub 2013/11/28. [PubMed: 24278360]
69. Zhao P, Wang C, Liu W, Wang F. Acute liver failure associated with traditional Chinese medicine: report of 30 cases from seven tertiary hospitals in China*. *Crit Care Med.* 2014; 42(4):e296–9. Epub 2013/12/18. [PubMed: 24335449]
70. Elinav E, Pinsker G, Safadi R, Pappo O, Bromberg M, Anis E, et al. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol.* 2007; 47(4):514–20. Epub 2007/08/19. [PubMed: 17692424]
71. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. *Liver Int.* 2012; 32(10):1543–56. Epub 2012/08/30. [PubMed: 22928722]
72. Johannsson M, Ormarsdottir S, Olafsson S. Hepatotoxicity associated with the use of Herbalife. *Laeknabladid.* 2010; 96(3):167–72. Epub 2010/03/04. *Liffraskadi tengdur notkun a Herbalife.* [PubMed: 20197595]

73. Appelhans K, Frankos V, Shao A. Misconceptions regarding the association between Herbalife products and liver-related case reports in Spain. *Pharmacoepidemiol Drug Saf.* 2012; 21(3):333–4. author reply 5. Epub 2012/03/13. [PubMed: 22407600]
74. Appelhans K, Najeeullah R, Frankos V. Letter: retrospective reviews of liver-related case reports allegedly associated with Herbalife present insufficient and inaccurate data. *Aliment Pharmacol Ther.* 2013; 37(7):753–4. Epub 2013/03/06. [PubMed: 23458533]
75. Reddy KR, Bunchorntavakul C. Letter: retrospective reviews of liver-related case reports allegedly associated with Herbalife present insufficient and inaccurate data--authors' reply. *Aliment Pharmacol Ther.* 2013; 37(7):754–5. Epub 2013/03/06. [PubMed: 23458534]
76. Klontz KC, DeBeck HJ, LeBlanc P, Mogen KM, Wolpert BJ, Sabo JL, et al. The Role of Adverse Event Reporting in the FDA Response to a Multistate Outbreak of Liver Disease Associated with a Dietary Supplement. *Public Health Rep.* 2015; 130(5):526–32. Epub 2015/09/04. [PubMed: 26327730]
77. Johnston DI, Chang A, Viray M, Chatham-Stephens K, He H, Taylor E, et al. Hepatotoxicity associated with the dietary supplement OxyELITE Pro - Hawaii, 2013. *Drug Test Anal.* 2016; 8(3-4):319–27. Epub 2015/11/06. [PubMed: 26538199]
78. 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(45):6999–7004. Epub 2008/12/06. [PubMed: 19058338]
79. Fong TL, Klontz KC, Canas-Coto A, Casper SJ, Durazo FA, Davern TJ 2nd, et al. Hepatotoxicity due to hydroxycut: a case series. *Am J Gastroenterol.* 2010; 105(7):1561–6. Epub 2010/01/28. [PubMed: 20104221]
80. Linnebur SA, Rapacchietta OC, Vejar M. Hepatotoxicity associated with chinese skullcap contained in Move Free Advanced dietary supplement: two case reports and review of the literature. *Pharmacotherapy.* 2010; 30(7):750, 258e–62e. Epub 2010/07/01. [PubMed: 20586134]
81. Yang L, Aronsohn A, Hart J, Jensen D. Herbal hepatotoxicity from Chinese skullcap: A case report. *World J Hepatol.* 2012; 4(7):231–3. Epub 2012/08/03. [PubMed: 22855699]
82. Dhanasekaran R, Owens V, Sanchez W. Chinese skullcap in move free arthritis supplement causes drug induced liver injury and pulmonary infiltrates. *Case Reports Hepatol.* 2013; 2013:965092. Epub 2013/01/01. [PubMed: 25431706]
83. Haouzi D, Lekehal M, Moreau A, Moulis C, Feldmann G, Robin MA, et al. Cytochrome P450-generated reactive metabolites cause mitochondrial permeability transition, caspase activation, and apoptosis in rat hepatocytes. *Hepatology.* 2000; 32(2):303–11. Epub 2000/08/01. [PubMed: 10915737]
84. Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. *Arch Intern Med.* 1997; 157(8):913–9. Epub 1997/04/28. [PubMed: 9129552]
85. Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Gastroenterology.* 1999; 117(5):1234–7. Epub 1999/10/27. [PubMed: 10535888]
86. Kienle GS, Grugel R, Kiene H. Safety of higher dosages of *Viscum album* L. in animals and humans--systematic review of immune changes and safety parameters. *BMC Complement Altern Med.* 2011; 11:72. Epub 2011/08/30. [PubMed: 21871125]
87. Thomassen D, Slaterry JT, Nelson SD. Menthofuran-dependent and independent aspects of pulegone hepatotoxicity: roles of glutathione. *J Pharmacol Exp Ther.* 1990; 253(2):567–72. Epub 1990/05/01. [PubMed: 2338648]
88. Neff GW, Reddy KR, Durazo FA, Meyer D, Marrero R, Kaplowitz N. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. *J Hepatol.* 2004; 41(6):1062–4. Epub 2004/12/08. [PubMed: 15582145]

Key Points

- The increase in the use of herbal and dietary supplements (HDS) and a growing awareness of the potential for these agent to cause liver injury has been associated with an increase in reports of HDS associated hepatotoxicity.
- Limited regulatory oversight, inaccurate product labeling, adulterants and inconsistent sourcing of constituent ingredients may all contribute to the potential for toxicity.
- The spectrum of HDS induced liver injury is diverse and the outcome may vary from transient liver test abnormalities to acute hepatic failure requiring liver transplantation, or resulting in death.
- The most commonly implicated products include bodybuilding and weight loss products. There are no validated standardized tools to establish the diagnosis, but some HDS products do have a clear clinical signature that can make diagnosis almost certain.

Trend test for HDS $p = .0007$

Trend test for body building HDS: $P=0.007$

Trend test for Non bodybuilding HDS: $P=0.05$

Figure 1.

Increase of the proportion of enrolled DILI patients due to HDS products in the DILIN prospective study.

Light gray bar represents medications, medium gray bar represents nonbodybuilding HDS, and dark gray bar represents bodybuilding HDS. From Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology*. 2014;60(4):1399-408, with permission.

Figure 2.

This patient presented with jaundice and moderately severe subacute hepatitis. She denied any drug or HDS ingestion on repeated questioning over several visits. A liver biopsy was performed as liver tests were slow to improve, and was suspicious for hepatotoxicity. The patient was asked again about ingestions and she admitted that she was taking “one or two” HDS products. She wheeled this suitcase in to her next visit and admitted that she was regularly using all the products in the bag.

Figure 3.

A patient was referred with abnormal liver tests. He readily admitted to using HDS and brought in all of the products seen here. This illustrates the challenges of ascribing causality to a specific agent. (Courtesy of Dr. Victor Navarro)

Table 1

Use and mechanism of specific HDS products

Herbals	Common use	Mechanism and comments	References
Anabolic steroids	bodybuilding, weight training, or athletics	unknown	(40)
Black cohosh (<i>Cimicifuga/Actaea racemosa</i>)	joint aches, myalgia and menopausal symptoms	unknown possibly adulterated with <i>Actaea pachypoda</i> Ell. (white cohosh) and <i>Actaea podocarpa</i> DC. (yellow cohosh)	(46)
Chaparral (<i>Larrea tridentata</i>)	antioxidant properties, anti-inflammatory, liver disease, skin disorders	unknown possibly, interference with cyclo-oxygenase or CYP450, estrogen-like activity	(84)
Green tea extracts (<i>Camellia sinensis</i>)	weight loss	epigallocatechin gallate (EGCG) toxicity is possibly heightened in individuals with a genetic predisposition	(54)
Pyrrolizidine alkaloids/Comfrey (<i>Senecio</i> , <i>Symphytum</i>)	natural home remedy	hepatic sinusoidal cells are damaged, ultimately resulting in sinusoidal obstruction syndrome	(55, 64)
Germander (<i>Teucrium chamaedrys</i>)	dyspepsia, obesity, diabetes and abdominal colic	CYP3A4 dependent alkylation of microsomal protein leading to autoantibody formation	(47-49)
Greater celandine (<i>Chelidonium majus</i>)	dyspepsia	unknown	(85)
Kava Kava (<i>Piper methysticum</i>)	gall bladder disease, biliary colic, cholelithiasis, and jaundice	immunoallergic and idiosyncratic factors, including CYP2D6 deficiency	(65, 66)
Mistletoe (<i>Viscum Album</i>)	asthma, infertility, hypertension	mistletoe lectins have immunostimulating properties and a strong dose-dependent cytotoxic activity	(86)
Pennyroyal (<i>Mentha pulegium</i> , <i>Hedeoma pulegoides</i>)	abortifacient	oxidation of pulegone by cytochrome P450 into menthofuran, depletion of glutathione	(87)
Skullcap (<i>Scutellaria baicalensis</i>)	arthritic symptoms	CYP3A dependent apoptosis demonstrated in isolated rat hepatocytes	(80-82)
Jin Bu Huan	sedation, analgesic	adulteration with other plant genera	(38)
Ma huang	stimulant, weight loss	idiosyncratic ephedrine alkaloid toxicity	(88)

Table 2

Use and mechanism of specific HDS proprietary mixes

Proprietary mixes	Common use	Mechanism and comments	References
Herbalife	weight-loss or improvement of well-being	wide range of different products with listed and unlisted ingredients hepatotoxicity potentially due to contamination with <i>Bacillus subtilis</i> in some cases	(39)
OxyELITE Pro	weight loss	hepatotoxicity emerged after reformulation with synthetic aegeline product was recalled	(18, 24)
Hydroxycut	weight loss	different products, changing formulations voluntarily recalled in 2009	(79)
Move Free Advanced	<i>See skullcap</i> , table 1		(80-82)
SlimQuick	weight loss, <i>see green tea extracts</i> , table 1		(54)