Introduction

Herbal and dietary supplements (HDS) are commonly used by many people, both healthy and with specific ailments. The “well” HDS user often seeks to preserve health or promote a healthier lifestyle. The ailing HDS user seeks to supplement conventional therapies, hoping to achieve better health, or even to substitute for prescribed medications, with the perception that HDS are safe and as effective. It is estimated that over 40% of the U.S. population uses alternative therapies of some kind, most commonly HDS. Up to 40% of patients attending liver clinics also use supplements. Alarmingly, however, most patients who use HDS do not reveal this to their primary care provider. Moreover, it is not uncommon for providers to fail to ascertain a history of HDS use from their patients. Users of HDS tend to be Asians, younger, highly educated, and more health conscious than nonusers. The most common reasons for their use include obesity/weight loss, body building, menopausal symptoms, gastrointestinal disorders such as indigestion or constipation, liver disease, and neurological complaints such as headache and migraines.

Background

Herbal and dietary supplements are considered foods, and are defined as products taken by mouth that contain a dietary ingredient intended to supplement the diet. These ingredients include vitamins, minerals, herbs and other botanicals, amino acids, enzymes, organ tissues, and metabolites. However, since HDS are not drugs, they are regulated differently than conventional pharmaceuticals. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA) (http://www.fda.gov/Food/DietarySupplements/default.htm), manufacturers of HDS are responsible for the safety of their
products, but need not have FDA approval before marketing. More recently, the Current Good Manufacturing Practices–Dietary Supplement Act (2007)–establishes the minimum standards for manufacturing, packaging, labeling, and holding, and is intended to ensure the identify, purity, quality, strength, and composition. Manufacturers are not required to conduct preclinical safety and efficacy assessments prior to marketing. The FDA’s specific responsibility is to determine if an HDS is unsafe, after which it can take action to recommend withdrawal from the market. Concern over a specific HDS or ingredient usually is triggered from reports of adverse events which may come from MEDWATCH or the manufacturer, which is statutorily compelled to alert the FDA of such events about which it becomes aware.

Hepatotoxicity

The hepatotoxic potential of HDS has been recognized for many years. There are no reliable population-based statistics for the incidence of toxicity attributable to HDS in the United States, although the true incidence is likely to be very low. In the Drug Induced Liver Injury Network, HDS were implicated in approximately 10% of cases, but this rate appears to be increasing and most recently was more than 16% of cases. As discussed in the various HDS records within LiverTox, many single herbs have been implicated in liver toxicity. However, most currently available HDS comprise complex mixtures of ingredients and, although the FDA requires that a product label accurately reflect the contents, reports exist of product contamination and unlabeled ingredients. Reported contaminants include heavy metals, pharmaceuticals, microbial products, and pesticides. Further, HDS are vulnerable to variation in the quality or strength of ingredients, depending upon the time and conditions of harvest, as well as the part of the plant that is used for the product (for instance, leaf vs root vs. stem). Finally, analytical phytochemistry of HDS products implicated in causing liver injury often reveals adulteration of the product and sometimes mislabeling and absence of the
botanical listed on the label and presence of a related or unrelated herbal that may be the hepatotoxic agent.

The diagnosis of HDS associated liver injury is predicated upon the usual principles of causality assessment, including establishing a chronology which implicates the HDS as having been taken before the onset of injury, exclusion of other causes of liver disease, and the response to withdrawal. The published experience with HDS associated liver toxicity is growing, but limited for many of the myriad available products. As in conventional pharmaceuticals, the confidence with which a diagnosis of liver injury is made depends, to a great extent, on the number of previously reported and published cases. Thus, time and experience will lead to more precise attribution of liver injury to HDS. Even for those HDS in which significant published experience on toxicity exists, the attribution of injury to a specific ingredient of the HDS is difficult, due to the complexity of the mixture. Arguably, the most surmountable obstacles to diagnosing HDS associated liver injury include the provider’s foresight in obtaining a complete supplement use history and the patient’s willingness to disclose their use.

Finally, chemical analysis of the implicated product can be very valuable in assigning causality, particularly for botanicals that have not been commonly implicated in causing liver disease as such analysis may identify the presence of a well established hepatotoxic agent. Examples of contaminants found in herbal preparations include germander in products labeled as being skullcap and various Asian Actaea in products labeled as black cohosh.

Mechanism of Injury

The mechanism of liver injury due to HDS is, in the majority of cases, unknown. Most cases appear to be idiosyncratic and the clinical picture, including histology, is no different than that which is seen in conventional drug associated liver injury.
However, some HDS are associated with a specific type of injury; for example, pyrrolizidine alkaloids which have been reported to lead to sinusoidal obstruction syndrome. As learned through the experience of the Drug Induced Liver Injury Network, it appears that most patients who sustain liver injury attributable to HDS manifest a hepatocellular pattern of injury.

Outcome and Management

The principles of management of HDS associated liver injury are the same as those exercised for injury induced by conventional pharmaceuticals. Patients must be advised to cease all supplement use, and be monitored for signs of significant liver dysfunction. In the most severe circumstances, these signs include coagulopathy, encephalopathy, ascites, and jaundice. Most patients, however, may have mild or no symptoms associated with elevated liver enzymes. In these cases, it is no less important to advise the patient to stop HDS use, as limited experience in most cases, as well the factors which are unique to HDS (contamination, variability), prevent providers from predicting the course of liver injury with great confidence.

The following HDS products are specifically discussed in LiverTox.

- Aloe Vera
- Black Cohosh
- Cascara
- Chamomile
- Chaparral
- Chinese and Other Asian Herbal Medicines
  - Ba Jiao Lian
  - Chi R Yun
  - Jin Bu Huan
  - Ma Huang [Ephedra]
  - Sho Saiko To and Dai Saiko To
  - Shou Wu Pian
- Chondroitin
- Comfrey
- Crofelemer
- Ephedra
- Fenugreek
- Flavocoxid
- Germander
- Ginkgo
- Ginseng
- Glucosamine
- Greater Celandine
- Green Tea
- Hoodia
- Hops
- Horse Chestnut
- Hyssop
- Kava Kava
- Kratom
- Lavender
- Margosa Oil
- Melatonin
- Milk Thistle
- Noni
- Passionflower
- Pennyroyal Oil
- Red Yeast Rice
- Resveratrol
- Saw Palmetto
- Senna
- Skullcap
- St. John's Wort
- Usnic Acid
- Valerian
- Yohimbine
- Multi-Ingredient Nutritional Supplements
  - Herbalife
  - Hydroxycut
  - Move Free
  - OxyELITE Pro
  - SLIMQUICK


7. De Smet PA. Herbal remedies. N Engl J Med 2002; 347: 2046-56. PubMed Citation (Brief review of herbal remedies discussing their growing use, lack of regulation, problems of variability in content, quality, safety, potential adulterants and adverse events including hepatotoxicity, efficacy and special needs for prospective randomized controlled trials to define these factors; specific discussion of hawthorn, saw palmetto, ginkgo and St. John's Wort).


9. Pittler MH, Ernst E. Systematic review: hepatotoxic events associated with herbal medicinal products. Aliment Pharmacol Ther 2003; 18: 451-71. PubMed Citation (Systematic review of published cases of hepatotoxicity due to herbal medications listing 52 case reports or case series, most common agents being celandine [3], chaparral [3], germander [8], Jin Bu Huan [3], kava [1], Ma Huang [3], pennyroyal oil [1], skullcap [2], Chinese herbs [9], valerian [1]).


11. Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. Med J Aust 2004; 181: 222-5. PubMed Citation (Review of hepatotoxicity of herbal medications discussing their rising use in Australia and the problems of quality and safety, separating adverse events into "predictable" reactions and "idiosyncratic" reactions and stressing the need for further research, regulation and patient education).

12. Lenz TL, Hamilton WR. Supplemental products used for weight loss. J Am Pharm Assoc 2004; 44: 59-67. PubMed Citation (At least 50 herbal and dietary supplements have
been promoted for weight loss, but none have strong clinical evidence of efficacy and several are toxic [ephedra and green tea]).

13. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed Citation (Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] for herbal medications).


17. García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. [Liver injury induced by “natural remedies”: an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008; 100: 688-95. Spanish. PubMed Citation (Among 521 cases of drug induced liver injury submitted to Spanish registry, 13 [2%] were due to herbals, including green tea extracts in 3, cascara in 2, and horse chestnut, copalchi, chitosan, senna, valerian, kava, phytosoy and biosoy in 1 case each).


19. Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-82. PubMed Citation (Review of the problems of causality assessment in herbal and dietary supplement [HDS] associated liver disease, including the variable clinical presentations, the complexity and lack of information on their components, absence of controlled trials demonstrating safety and efficacy, the possibility of contamination or incorrect labeling and frequent underreporting of herbal use by patients. The regulation of HDS is under DSHEA which requires manufacturers to determine safety and prohibits claims of efficacy in treating specific diseases. The US Pharmacopeia sets standards for food and drugs, and includes HDS; HDS induced liver injury is a growing problem and current accounts for at least 10% of cases of acute liver injury due to medications).

20. Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. Pharmacoepidemiol Drug Saf 2009; 18: 1039-47. PubMed Citation (Review of 778 spontaneous reports of adverse reactions to herbals to Swedish Registry found 31 with increased liver enzymes, 26 with elevated aminotransferase levels, 22 with mixed liver reaction and 12 with hepatitis; agents implicated in causing liver injury included valerian, ginseng, green tea, and aloe vera).

21. Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed Citation (Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals, including several herbal mixtures, usnic acid, Ma Huang, black cohosh, and Hydroxycut products).

23. Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012; 32: 1543-56. PubMed Citation (A systematic compilation of all publications on the hepatotoxicity of specific herbas identified 185 publications on 60 different herbas, herbal drugs and supplements, and a discussion of the difficulties of causality attribution and appeal for publications to be more complete in presenting information on the liver injury and its link to herb preparations).


26. Björnsson ES, Bergmann OM, Björnsson 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: 1419-25. PubMed Citation (In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 15 [16%] due to herbal and dietary supplements).


center in Turkey, 10 [12%] of which were due to HDS products, including 7 due to Teucrium polium [mountain germander] and 3 to green tea extract.

30. Teschke R, Genthner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: Analysis of cases with initially reported positive re-exposure tests. Dig Liver Dis 2014; 46: 264-9. PubMed Citation (Reanalysis of 34 published cases of liver injury due to herbal medications in which there was a reported positive rechallenge, finding only 21 [62%] fulfilled the criteria of a positive rechallenge using RUCAM, the others having inconsistent [18%] or incomplete data [21%]).

31. de Oliveira AV, Rocha FT, Abreu SR. Acute liver failure and self-medication. Arq Bras Cir Dig 2014; 27: 294-7. PubMed Citation (Review of published literature on acute liver failure associated with self-medication identified cases related to acetaminophen, GTE, linoleic acid, rhamnus purshianus [Fitosoja] and usnic acid).

32. Teschke R, Zhang L, Melzer L, Schulze J, Eickhoff A. Green tea extract and the risk of drug-induced liver injury. Expert Opin Drug Metab Toxicol 2014; 10: 1663-76. PubMed Citation (Review of literature on whether green tea intake might increase the risk of liver injury from other drugs, via drug-herb interactions, concludes that there is no evidence that it does).


Citation (Extensive review of possible beneficial as well as harmful effects of herbal products on the liver).


40. Zheng EX, Navarro VJ. Liver injury from herbal, dietary, and weight loss supplements: a review. J Clin Transl Hepatol 2015; 3: 93-8. PubMed Citation (Review of literature on liver injury due to HDS products used for weight loss, focusing upon the case series of liver injury attributed to green tea as well as the commercial products that appear to contain it such as Herbalife and Hydroxycut, the injury of which was predominantly hepatocellular (acute hepatitis-like) and had a significant mortality rate).


Marcus DM. Dietary supplements: What's in a name? What's in the bottle? Drug Test Anal 2016; 8 (3-4): 410-2. PubMed Citation (Commentary on regulation of HDS products concludes: "the marketing of botanical supplements is based on unfounded claims that they are safe and effective", and "there is no reason to take herbal medicines whose composition and benefits are unknown and whose risks are evident").

42. Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1

43. Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 472-501. PubMed Citation (Description of an online compendium of cases of liver toxicity attributed to HDS products, lists at least 46 published cases of green tea associated liver injury and concludes that green tea may warrant a warning label).


45. de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed Citation (Review of the frequency, clinical features, patterns of injury and outcomes of HDS hepatotoxicity with specific mention of anabolic steroids, black cohosh, germander, green tea, kava, pyrrolizidine alkaloids and proprietary multiingredient nutrition supplements [MINS]).


47. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology 2017; 65: 363-73. PubMed Citation (Review of the problems of liver injury and HDS products and challenges for future research concludes that stronger regulations are needed to address the increasing number of cases of HDS induced liver injury, particularly those linked to use of multiingredient dietary supplements).