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Herbal and Dietary Supplements

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OVERVIEW

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
- Ashwagandha
- Astragalus

- Bilberry
- Black Cohosh
- Butterbur
- Cascara
- Cat's Claw
- 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
- Echinacea
- Ephedra
- Fenugreek
- Flavocoxid
- Garcinia Cambogia
- Germander
- Ginkgo
- Ginseng
- Glucosamine
- Greater Celandine
- Green Tea
- Hoodia
- Hops
- Horse Chestnut
- Hyssop
- Kava Kava
- Kratom
- Lavender
- Maca
- Margosa Oil
- Melatonin
- Milk Thistle
- Noni
- Passionflower
- Pennyroyal Oil
- Red Yeast Rice
- Resveratrol
- Saw Palmetto
- Senna
- Skullcap
- Spirulina
- St. John's Wort

- Turmeric
- Usnic Acid
- Valerian
- Yohimbine
- Multi-Ingredient Nutritional Supplements
  - Herbalife
  - Hydroxycut
  - Move Free
  - OxyELITE Pro
  - SLIMQUICK

ANNOTATED BIBLIOGRAPHY

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(Single author review of hepatotoxicity published in 1999; herbal medications covered in 3 pages at the end of a chapter on miscellaneous drugs, focusing on pyrrolizidine containing preparations, Chinese herbs, germander, chaparral, valerian, skullcap, amanita, and pennyroyal).

Liu LU, Schiano TD. Hepatotoxicity of herbal medicines, vitamins and natural hepatotoxins. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 733-54.

(Review of hepatotoxicity published in 2007; HDS are covered in a 22 page chapter).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58. *(Review of hepatotoxicity of herbal and dietary supplements [HDS]*

published in 2013; HDS are covered in a 26 page chapter).

Larrey D. Hepatotoxicity of herbal remedies. J Hepatol 1997; 52: 97-103. PubMed PMID: 9138129.

(Review of hepatotoxicity of herbals focusing upon pyrrolizidine alkaloids, germander and Chinese herbal medications).

Stickel F, Egerer G, Seitz HK. Hepatotoxicity of botanicals. Public Health Nutr 2000; 3: 113-24. PubMed PMID: 10948380.

(Review of hepatotoxicity of botanicals with specific discussion of Chinese herbals, germander, pyrrolizidine alkaloids, chaparral, and mushroom poisoning).

Stedman C. Herbal hepatotoxicity. Semin Liver Dis 2002; 22: 195-206. PubMed PMID: 12016550.

(Review of HDS hepatotoxicity and description of patterns of liver injury, including discussion of clinical patterns, potential risk factors, and herb-drug interactions with specific discussion of pyrrolizidine alkaloids, germander, Chinese herbs, chaparral, greater celandine, pennyroyal, herbal laxatives, and kava).

De Smet PA. Herbal remedies. N Engl J Med 2002; 347: 2046-56. PubMed PMID: 12490687.

(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, gingko and St. John's Wort).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. Clin Liver Dis 2003; 7: 453-73. PubMed PMID: 12879994.

(Review of HDS associated hepatotoxicity, including common patterns of presentation and specific discussion of pyrrolizidine alkaloids, chaparral, germander, pennyroyal, skullcap, valerian, kava, Chinese herbals, greater celandine, and Lipokinetix).

Pittler MH, Ernest E. Systematic review: hepatotoxic events associated with herbal medicinal products. Aliment Pharmacol Ther 2003; 18: 451-71. PubMed PMID: 12950418.

(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]).

Pak E, Esrason KT, Wu VH. Hepatotoxicity of herbal remedies: an emerging dilemma. Prog Transplant 2004; 15: 91-6. PubMed PMID: 15264453.

(Review of hepatotoxicity of herbal medications stressing the recent rise in numbers of cases, with literature review of comfrey, chaparral, germander, Ma Huang, Jin Bu Huan, greater celandine, cascara, kava and St. John's wort).

Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. Med J Aust 2004; 181: 222-5. PubMed PMID: 15310261.

(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).

Lenz TL, Hamilton WR. Supplemental products used for weight loss. J Am Pharm Assoc 2004; 44: 59-67. PubMed PMID: 14965155.

(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]).

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 PMID: 15390328.

(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).

Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. J Hepatol 2005; 43: 901-10. PubMed PMID: 16171893.

(Topical review, highlighting Chinese herbs, pyrrolizidine alkaloids, germander, greater celandine, kava, and chaparral, among others; insights on diagnosis and management are offered).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al.; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005; 129: 512-21. PubMed PMID: 16083708.

(Reports of drug induced liver injury to a Spanish network: among 570 cases, herbal medications accounted for 9 [1.5%]).

Seeff LB. Herbal hepatotoxicity. Clin Liver Dis 2007; 11: 577-96. PubMed PMID: 17723921.

(Review of HDS associated hepatotoxicity, with review of the literature and details of hepatic injury for black cohosh, chaparral, Chinese herbs, comfrey and pyrrolizidine alkaloids, germander, celandine, kava, mistletoe, pennyroyal, skullcap and valerian).

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 PMID: 19159172.

(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).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbals and dietary supplements, prominent agents being green tea, androgenic steroids, and miscellaneous Hydroxycut and Herbalife products).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. Semin Liver Dis 2009; 29: 373-82. PubMed PMID: 19826971.

(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).

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 PMID: 19650152.

(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).

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 PMID: 20949552.

(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).

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011; 31: 595-605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from herbals and dietary supplements focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, noni juice, Chinese herbs, vitamin A and anabolic steroids).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int 2012; 32: 1543-56. *(A* PubMed PMID: 22928722.

systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, 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 herbal preparations).

Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. Aliment Pharmacol Ther 2013; 37: 3-17. PubMed PMID: 23121117.

(Systematic review of literature on HDS associated liver injury with specific discussion of Ayurvedic products, chaparral, Chinese herbals, germander, greater celandine, green tea, Herbalife and Hydroxycut products, kava, pennyroyal oil, pyrrolizidine alkaloids and herb-drug interactions).

Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. Eur J Gastroenterol Hepatol 2013; 25: 1093-8. PubMed PMID: 23510966.

(Review of the literature of case series of suspected HDS related liver injury found evidence of other explanations for the liver injury in 19 of 23 publications involving 278 of 573 patients [49%], and that these other diagnoses weakened the causality assessment in most instances).

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 PMID: 23419359.

(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).

Licata A, Macaluso FS, Craxì A. Herbal hepatotoxicity: a hidden epidemic. Intern Emerg Med 2013; 8: 13-22. PubMed PMID: 22477279.

(Review and commentary on herbal hepatotoxicity with specific focus on ephedra, germander, kava, chapararal, black cohosh, greater celandine, and Herbalife, Hydroxycut and LipoKinetix products).

Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. Clin Liver Dis 2013; 17: 715-35. PubMed PMID: 24099027.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment).

Dağ MS, Aydınlı M, Oztürk ZA, Türkbeyler IH, Koruk I, Savaş MC, Koruk M, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014; 25: 41-5. PubMed PMID: 24918129.

(Between 2008 and 2012, 82 patients with drug or herbal supplement induced liver injury were seen at a single referral 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).

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 PMID: 24315480.

(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%]).

de Oliveira AV, Rocha FT, Abreu SR. Acute liver failure and self-medication. Arq Bras Cir Dig 2014; 27: 294-7. PubMed PMID: 25626943.

(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).

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 PMID: 25316200.

(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).

Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, Reddy KR, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014; 60:1399-408. PubMed PMID: 25043597.

(Among 85 cases of HDS associated liver injury [not due to anabolic steroids] enrolled in a US prospective study between 2004 and 2013, the single most commonly implicated herbal agent was green tea extract).

Rossi S, Navarro VJ. Herbs and liver injury: a clinical perspective. Clin Gastroenterol Hepatol 2014; 12: 1069-76. PubMed PMID: 23924877.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and assessing causality).

Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis 2014; 34: 172-93. PubMed PMID: 24879982.

(Review of HDS induced liver injury including regulatory problems, difficulties in diagnosis and causality assessment).

Korth C. Drug-induced hepatotoxicity of select herbal therapies. J Pharm Pract 2014; 27: 567-72. PubMed PMID: 25546878.

(Review of liver injury due to selected HDS discusses the literature implicating kava, green tea, germander, pyrrolizidine alkaloids and Herbalife products).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015; 148: 517-32. PubMed PMID: 25500423.

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

Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol. 2015; 89: 851-65. PubMed PMID: 25680499.

(Extensive review of liver injury due to HDS).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a prospective database between 2004 and 2012, HDS were implicated in 145 [16%], the single major herbal cause being green tea extract).

Zheng EX, Navarro VJ. Liver injury from herbal, dietary, and weight loss supplements: a review. J Clin Transl Hepatol 2015; 3: 93-8. PubMed PMID: 26357638.

(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).

García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by dietary supplements: A tabular listing and clinical characteristics. Int J Mol Sci 2016; 17. pii: E537. PubMed PMID: 27070596.

(Listing of published cases of liver injury from HDS products).

Avigan MI, Mozersky RP, Seeff LB. Scientific and regulatory perspectives in herbal and dietary supplement associated hepatotoxicity in the United States. Int J Mol Sci 2016; 17: 331. PubMed Citation (Overview of the US

regulations regarding herbal and dietary supplements and role of FDA, Department of Agriculture, Federal Trade Commission and Office of Dietary Supplements of the NIH in assessment of safety of HDS products including actions taken against Hydroxycut, Lipokinetix and OxyELITE Pro when reports of liver injury appeared in postmarketing phase).

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").

Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. Food Chem Toxicol 2017; 107 (Pt A): 449-71. PubMed PMID: 27818322.

(Summary of the US regulations on safety and efficacy of herbal and dietary supplements).

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 PMID: 27402097.

(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).

Wong LL, Lacar L, Roytman M, Orloff SL. Urgent liver transplantation for dietary supplements: an under-recognized problem. Transplant Proc 2017; 49: 322-5. PubMed PMID: 28219592.

(Among 2048 adult liver transplants recipients enrolled in the Scientific Registry of Transplant Recipients [SRTR] between 2003 and 2015, 625 were done for acute hepatic necrosis due to drug induced liver injury, half being due to acetaminophen and the 4th most frequent cause [n=21] being HDS products).

de Boer YS, Sherker AH. Herbal and dietary supplement-induced liver injury. Clin Liver Dis 2017; 21: 135-49. PubMed PMID: 27842768.

(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]).

Vega M, Verma M, Beswick D, Bey S, Hossack J, Merriman N, Shah A, et al; Drug Induced Liver Injury Network (DILIN). The incidence of drug- and herbal and dietary supplement-induced liver injury: preliminary findings from gastroenterologist-based surveillance in the population of the State of Delaware. Drug Saf 2017; 40: 783-7. PubMed PMID: 28555362.

(A prospective, population based registry of cases of drug induced liver injury occurring in Delaware during 2014, identified 20 cases [2.7 per 100,000] overall, including 6 due to HDS products, all of which were proprietary multiingredient products).

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 PMID: 27677775.

(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).

INTERNET SITES WITH RELIABLE HDS INFORMATION

Internet searches will identify hundreds of websites with information on specific botanicals and nutritional supplements, but the quality of the information varies enormously and many websites offer only anecdotal and

unreliable testimonies to the benefits and offers for sale of the HDS. Fairly reliable and unbiased information on HDS can be obtained from the following US Government supported websites.

www.ods.od.nih.gov (The health information website of the Office of Dietary Supplements in the Office of the Director, National Institutes of Health)

www.nccih.nih.gov/health/supplements/wiseuse.htm (Information website of the National Center for Complementary and Integrative Health, National Institutes of Health)

www.nlm.nih.gov/medlineplus/druginfo/herb_All.html (Website of the National Library of Medicine's MedlinePlus)