CHAPTER 8
Herbal and dietary supplement induced liver injury

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ABSTRACT

The increase in the use of herbal and dietary supplements (HDS) over the last decades has been accompanied by 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 increases to fulminant hepatic failure resulting in death or requiring liver transplant. There are no validated standardized tools to establish the diagnosis, but some HDS products have a typical clinical signature that may help to identify HDS-induced liver injury.
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. 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 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. About half of the adult population in the United States reports having used at least one dietary supplement in the past month. These products are more commonly used by non-Hispanic whites, at older age and with higher levels of education. 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. 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. Nationally, it is estimated that 23,000 emergency department visits each year can be attributed to adverse effects associated with the use of HDS. 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, while in Iceland the number is approximately 16%. 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). 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).
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. 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. Recent examples of HDS products that were withdrawn from the market include OxyElite Pro in 2013 (caused acute liver failure) and Hydroxycut (hepatocellular injury with jaundice). In the European Union (EU), herbal and dietary supplements are regulated under the Traditional Herbals Medicine Products Directive 2004/24/EC. 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, whereas...
herbal medical products are overseen by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA). 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.

**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. 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. 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.25 The score is derived from 10 simple questions that can add up to a total score that ranges from -4 to 14.25 Although widely used, this system was shown to have a limited applicability in estimating liver injury due to drugs.26 Instead, they found that the Roussel Uclaf Causality Assessment Method (RUCAM), which is more discussed in greater detail elsewhere in this issue, performed better.26-29

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.
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 (\(\frac{[\text{ALT/ULN}]}{[\text{Alk P/ULN}]}\)), 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.\(^{14, 24, 30-34}\) 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 hepatoxicity 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\textsuperscript{35})(Tables 1 and 2). 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.\textsuperscript{36} 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 \textit{Polygala chinensis} as its single effective ingredient, but were found to contain levo-tetrahydropalmatine, which is found in the plant genera \textit{Stephania} and \textit{Corydalis} but not in the genus \textit{Polygala}.\textsuperscript{37} 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 \textit{Bacillus subtilis} as a potential cause for the products’ hepatotoxicity profile\textsuperscript{38}.

**HEPATOTOXICITY ASSOCIATED WITH SPECIFIC HDS:**

**Anabolics:** Marketed anabolic steroids are generally synthetic chemicals and are not HDS as strictly defined.\textsuperscript{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.\textsuperscript{15,39} 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” [Observation made by Dr. Jay H. Hoofnagle in DILIN Causality Assessment, 2013]). Patients should be warned that the use of these agents may be illegal.
Table 1. Use and mechanism of specific HDS products

<table>
<thead>
<tr>
<th>Herbals</th>
<th>Common use</th>
<th>Mechanism and comments</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Anabolic steroids</td>
<td>bodybuilding, weight training, or athletics</td>
<td>unknown</td>
<td>39</td>
</tr>
<tr>
<td>Black cohosh (Cimicifuga/Actaea racemosa)</td>
<td>joint aches, myalgia and menopausal symptoms</td>
<td>unknown possibly adultrated with Actaea pachypoda Ell. (white cohosh) and Actaea podocarpa DC. (yellow cohosh)</td>
<td>45, 45</td>
</tr>
<tr>
<td>Chaparral (Larrea tridentata)</td>
<td>antioxidant properties, anti-inflammatory, liver disease, skin disorders</td>
<td>unknown possibly, interference with cyclo-oxygenase or CYP450, estrogen-like activity</td>
<td>83</td>
</tr>
<tr>
<td>Green tea extracts (Camellia sinensis)</td>
<td>weight loss</td>
<td>epigallocatechin gallate (EGCG) toxicity is possibly heightened in individuals with a genetic predisposition</td>
<td>53</td>
</tr>
<tr>
<td>Pyrrolizidine alkaloids/Comfrey (Senecio, Symphytum)</td>
<td>natural home remedy</td>
<td>hepatic sinusoidal cells are damaged, ultimately resulting in sinusoidal obstruction syndrome</td>
<td>54, 55</td>
</tr>
<tr>
<td>Germander (Teucrium chamaedrys)</td>
<td>dyspepsia, obesity, diabetes and abdominal colic</td>
<td>CYP3A4 dependent alkylation of microsomal protein leading to autoantibody formation</td>
<td>46-48</td>
</tr>
<tr>
<td>Greater celandine (Chelidonium majus)</td>
<td>dyspepsia</td>
<td>unknown</td>
<td>84</td>
</tr>
<tr>
<td>Kava Kava (Piper methysticum)</td>
<td>gall bladder disease, biliary colic, cholelithiasis, and jaundice</td>
<td>immunoallergic and idiosyncratic factors, including CYP2D6 deficiency</td>
<td>64, 65</td>
</tr>
<tr>
<td>Mistletoe (Viscum Album)</td>
<td>asthma, infertility, hypertension</td>
<td>mistletoe lectins have immunostimulating properties and a strong dose-dependent cytotoxic activity</td>
<td>85</td>
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<tr>
<td>Pennyroyal (Mentha pulegium, Hedeoma pulegoides)</td>
<td>abortifacient</td>
<td>oxidation of pulegone by cytochrome P450 into menthofuran, depletion of glutathione</td>
<td>86</td>
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<tr>
<td>Skullcap (Scutellaria baicalensis)</td>
<td>arthritic symptoms</td>
<td>CYP3A dependent apoptosis demonstrated in isolated rat hepatocytes</td>
<td>79-81</td>
</tr>
<tr>
<td>Jin Bu Huan</td>
<td>sedation, analgesic</td>
<td>adulteration with other plant genera</td>
<td>37</td>
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<tr>
<td>Ma huang</td>
<td>stimulant, weight loss</td>
<td>idiosyncratic ephedrine alkaloid toxicity</td>
<td>87</td>
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<tr>
<td>Proprietary mixes</td>
<td>Common use</td>
<td>Mechanism and comments</td>
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<tr>
<td>Herbalife</td>
<td>weight-loss or improvement of well-being</td>
<td>wide range of different products with listed and unlisted ingredients</td>
<td>38</td>
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<tr>
<td></td>
<td></td>
<td>hepatotoxicity potentially due to contamination with Bacillus subtilis in some cases</td>
<td></td>
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<tr>
<td>OxyELITE Pro</td>
<td>weight loss</td>
<td>hepatotoxicity emerged after reformulation with synthetic aegeline</td>
<td>18, 23</td>
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<td></td>
<td></td>
<td>product was recalled</td>
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<tr>
<td>Hydroxycut</td>
<td>weight loss</td>
<td>different products, changing formulations</td>
<td>78</td>
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<td></td>
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<td>voluntarily recalled in 2009</td>
<td></td>
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<tr>
<td>Move Free Advanced</td>
<td>See skullcap, table 1</td>
<td></td>
<td>79-81</td>
</tr>
<tr>
<td>SlimQuick</td>
<td>weight loss, see green tea extracts, table 1</td>
<td></td>
<td>53</td>
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Table 2. Use and mechanism of specific HDS proprietary mixes
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, which has led to the publication of a cautionary statement by the US Dietary Supplement Information Expert Committee. 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. 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.

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. 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. Re-exposure to germander leads to rapid recurrence of the injury. 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. 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, galloatechin, 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. Epigallocatechin gallate (EGCG) is the most abundant green tea polyphenol, and is believed to be the most active and potent hepatotoxic component. 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.

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*.\(^{54}\) Reports from South Africa\(^{55}\) (*Senecio* -contaminated bread), India \(^{56}\) (*Crotalaria* -contaminated cereal), Afghanistan\(^{57}\) (*Heliotropium* -contaminated wheat) and the southwestern United States\(^{58-60}\) (*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.\(^{61}\) Interestingly, the pulmonary vascular bed is also sensitive to the effects of pyrrolizidine alkaloids.\(^{62}\) Sinosoidal 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.\(^{63}\)

**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.\(^{64-66}\) Both immunoallergic and idiosyncratic factors (including CYP2D6 deficiency), have been implicated.\(^{64, 65}\)

**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.\(^{67, 68}\)

**PROPRIETARY MIXES**

**Herbalife:** In 2004, a report by Elinav et al. implicated ingestion of Herbalife products in in 12 patients who developed DILI, manifest as acute fulminant hepatitis.\(^{69}\) 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.\(^{70}\) 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. Employees of Herbalife have aggressively criticized reports of Herbalife-associated hepatotoxicity, but their criticisms have been effectively rebutted.

**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%). In early 2013 the formula of OxyELITE Pro had been changed, substituting 1,3-Dimethylamylamine, which had been associated with cardiovascular toxicity, with aegeline. 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. 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. The product was recalled and the manufacturer was required to discontinue the distribution of OxyELITE Pro. 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.

**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. Several Hydroxycut products were voluntarily recalled in 2009, following a published FDA warning related to the use of Hydroxycut.

**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. 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. In one patient, pulmonary infiltrates developed simultaneous with the hepatotoxicity and resolved completely with cessation of the supplement. Diterpenoid compounds in *Scutellaria baicalensis*, have previously been shown to cause apoptosis in isolated rat hepatocytes, through reactive metabolites formed by CYP3A.
CONCLUSION

The increase in the use of herbal and dietary supplements and a growing awareness of the potential for these agents 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


55. Wilmot FC, Robertson GW. Senecio disease or cirrhosis of the liver due to Senecio poisoning. Lancet 1920:848-849.