

Hepatotoxicity Induced by Herbal and Dietary Supplements

Victor J. Navarro, MD¹ M. Isabel Lucena, MD²

¹Division of Hepatology, Einstein Medical Center, Philadelphia, Pennsylvania

²Clinical Pharmacology Service, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Malaga University, Malaga, Spain

Address for correspondence Victor J. Navarro, MD, Division of Hepatology, Einstein Medical Center, 5401 Old York Road, Suite 505, Philadelphia, PA 19141 (e-mail: NavarroV@einstein.edu).

Semin Liver Dis 2014;34:172–193.

Abstract

Herbals and dietary supplements (HDS) can cause hepatotoxicity. Regulation of HDS varies across the globe. In the United States, it is defined by a law that is now two decades old. More recent regulatory approaches in Europe still do not require testing for premarket safety. The true incidence of hepatotoxicity from HDS is unknown. The presentation is most often with a hepatocellular enzyme pattern, and the outcomes can be severe, leading to transplantation in some circumstances. The diagnosis of hepatotoxicity due to HDS is made in the same way as for drugs. However, patients often must be coaxed into revealing a history of use. No causality assessment approach is perfectly suited for hepatotoxicity from HDS, but the Roussel Uclaf Causality Assessment Method is most used. Future endeavors must focus on defining epidemiology, establishing an accepted nomenclature, and identifying culprit ingredients, predisposing host factors, and useful biomarkers for injury.

Keywords

- ▶ herbal and dietary supplements
- ▶ hepatotoxicity
- ▶ drug-induced liver injury

Herbals and dietary supplements (HDS) are consumed by nearly half of the American population and represent an enormous amount of commerce in the United States and worldwide. They are used for many reasons, but mostly as a means to improve one's overall feeling of well-being or appearance. In addition, HDS constitute an important part of traditional medical therapies in many parts of the world. Although these substances are often assumed to be natural and safe, there are many reports of liver injury resulting from HDS in the literature. Moreover, some products regarded as dietary supplements from a regulatory perspective may not be naturally occurring, as they are partly or wholly synthesized in the laboratory.

The value of some HDS is indisputable. Many naturally occurring substances have led to remarkable advances in human medicine. Among these include the isolation of opioids and alkaloids from the Papaver somniferum, digitalis derived from the foxglove plant and used for its cardiac effects, and quinine derived from cinchona bark and used

in the prevention and management of malaria. Yet, there are many concerns that may impact the safety of HDS and merit careful consideration. In this review, we will address hepatotoxicity, one of the most prominent manifestations of end-organ injury associated with HDS.

International Regulatory Frameworks for Herbal and Dietary Supplements

Since the topic of liver injury-induced by HDS was last presented in *Seminars*,¹ no significant regulation in the United States has been put forth that has had a substantial impact on the regulatory environment for HDS. The Dietary Supplement Health and Education Act (DSHEA) of 1994² remains the foundation for current regulation of HDS. The DSHEA was championed by Utah Senator Orin Hatch, whose original goal, as stated and defended in a recent speech to the Senate³ was "clarity, predictability, and a better understanding of what the FDA expected from industry and vice versa.

Issue Theme Drug-Induced Liver Injury; Guest Editors, Naga Chalasani, MD, and Paul H. Hayashi, MD, MPH

Copyright © 2014 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0034-1375958>. ISSN 0272-8087.

Table 1 U.S. Food and Drug Administration warnings and recalls for liver injury associated with herbal and dietary supplements

Product	Year	Comments
Comfrey	2001	Contained pyrrolizidine alkaloids
Lipokinetix	2001	Contained phenylpropanolamine, caffeine, yohimbine, diiodothyronine, and sodium usniate
Kava Kava	2002	Caused acute liver failure, hepatitis, cirrhosis
Hydroxycut	2009	Caused acute liver failure
Uprizing 2.0	2011	Found to contain Superdrol (anabolic steroid)
OxyElite Pro	2013	Caused acute liver failure

DSHEA provides an appropriate structure that balances the risks and benefits to consumers with continued access and affordability.” Since enactment of the DSHEA, warnings on several products as causes for liver injury have been issued by the Food and Drug Administration (FDA) (► **Table 1**). The most recent FDA warnings were for products containing multiple ingredients: Uprizing 2.0,⁴ which was found to contain undeclared synthetic steroids, and OxyElite Pro,⁵ which has been implicated in several cases of acute liver failure, some resulting in death or liver transplantation.

The DSHEA defines a dietary supplement as any product intended to supplement, but not substitute for diet. Dietary supplements may contain one or more ingredients that include vitamins, minerals, herbs, or other botanicals; amino acids; or extracts thereof. The law stipulates that a product's label must accurately reflect its contents. Ostensibly, the act provides the FDA with the authority to monitor the safety of marketed products. Unlike conventional pharmaceuticals, the DSHEA affords no assurance to the consumer as to the effectiveness of a product, maintenance of health, mitigation of disease, or to safety before it becomes available on the market. Subsequent legislation through the Final Rule for Dietary Supplement Current Good Manufacturing Practices (2007) still does not address assurances of safety to the consumer. Rather, this legislation only gives guidance to manufacturers on production standards, including an attestation that a product is free from adulteration and contamination. Essentially, the safety of any marketed dietary supplement is predicated upon a manufacturer's commitment to regulatory adherence. The burden of proof that a product caused harm or of a manufacturer's nonadherence to regulation rests upon the FDA.

One class of supplements, the medical foods, merit special mention because they require the supervision of a prescribing physician.⁶ However, they are still regarded as dietary supplements and recognized as such under the DSHEA. They are not regulated with the same rigor as are drugs, having no requirement for preclinical safety testing. A recent case series of liver injury resulting from the medical food Flavocoxib⁷ showed that this type of supplement has the capacity to induce liver injury.

Across the globe, regulation for HDS is quite varied. In the European Union, regulation is based upon the Traditional Herbs Medicine Products Directive 2004/24/EC.⁸ This regulation stipulates that products could be licensed for use

following a simplified registration procedure if there was an acceptably long period of demonstrated safety, specifically 15 years in the European Union (EU) and 30 years total, are not used parenterally, and do not require a medical prescription. After May 1, 2011, all unlicensed herbal medicinal products presented as having properties for treating or preventing disease in humans or where it has a pharmacological, immunological, or metabolic action must have been either marketed as medicines or withdrawn from the market. Unlike the FDA, the European Medicines Agency has the purview of herbal medicinal products only. Products considered food supplements or cosmetics are overseen by the European Food Safety Authority (EFSA), the appointed authority in the EU.

A Committee on Herbal Medicinal Products (HMPC),⁹ comprised of scientific experts in the field of herbal medicines from various disciplines, was established within the European Medicines Agency in September 2004 to develop a list of herbal substances, preparations, and combinations thereof that are used in traditional herbal medicinal products. The HMPC was also charged with creating a library of monographs containing information on composition, indications and contraindications, safety, and pharmacological properties for products with well-established use.¹⁰ In the United Kingdom (UK), the Herbal Medicines Advisory Committee was established to advise on the safety, quality, and efficacy of herbal medicinal products eligible for registration under the EU's regulation, as well as other unlicensed herbal products.¹¹

Beyond what is discussed above, there are no other broadly applied regulatory standards for HDS. In fact, the World Health Organization (WHO) in 2001 polled 191 member states and found that of 141 respondents, only 53 (38%) had some legislation governing HDS use.¹² The WHO has taken on the challenge of protecting and promoting public health and safety, globally,¹³ through improved regulation of herbal medicines with the creation of the International Regulatory Cooperation for Herbal Medicines (IRCH) in 2006.¹⁴

The Prevalence of Use and Commerce Attributable to Herbal and Dietary Supplements

The earliest reliable survey in the United States regarding the use of alternative medicine showed that 34% of those polled

used some form, 2.5% using herbal remedies.¹⁵ This stands in remarkable contrast to the more recent assessments which show that over half of the U.S. population uses supplements.^{16,17} A perusal of any local apothecary reveals the myriad supplement types and brands available to consumers. However, the most commonly used are multivitamins, and the most common motivations for use are health improvement and maintenance.¹⁸ Commercially available supplements are often marketed with creative and descriptive labels, and contain many ingredients blended and compounded into any one of several forms, including pills, capsules, powders, and elixirs.

Outside of the United States, limited statistics are available on the prevalence of use of HDS. It is estimated that 80% of the population uses herbals for medical treatment¹⁹ in Africa. In Europe, a survey published in 2009 showed great variability, both geographically and by gender. Prevalence of use among 10 European countries ranged from 2% of men in Greece to nearly 66% of women in Denmark.²⁰

The rise in use of HDS parallels an increase in commerce. Total sales of herbals and botanical dietary supplements in the United States have risen consistently over the past 9 years to \$5.5 billion in 2012.²¹ Globally, expenditures are expected to reach \$107 billion in 2017.²² Although accurate U.S. or global statistics on actual use of HDS are not available, one can infer that there has been an increase based on this rising HDS commerce.

Epidemiology of Liver Injury due to Herbal and Dietary Supplements

The epidemiology of liver injury due to HDS is largely unknown, but is likely to be strongly influenced by type of supplement, geography, and cultural acceptance. As stated earlier, use of HDS is an integral part of medical care in Africa. Similar commonplace use may be seen in Southeast Asia, and in Central and South America where there also is a long history of traditional herbal medicine.

The true prevalence and incidence of hepatotoxicity due to HDS cannot be estimated because of the unavailability of a denominator, the number of persons in a population who consume them. Accurate estimates based on sales are hindered by the many places where one can obtain HDS, such as health food stores, the Internet, and gymnasiums. Even in the elegant population-based prospective 2-year cohort study on the incidence of hepatotoxicity in Iceland in which HDS accounted for 16% of cases, the true impact of hepatotoxicity from natural products could not be determined.²³

Information on liver injury due to HDS has come mainly from published case reports or case series. However, inferences on its relative frequency could be made from prospective drug-induced liver injury (DILI) cohorts and retrospective databases that capture hepatotoxicity cases due to HDS (►Table 2). National and international DILI registries such as U.S. Drug-Induced Liver Injury Network (DILIN), the Spanish DILI Registry, and Spanish-Latin American DILI network (SLATINDILI) found 9%, 6%, and 8% of their liver injury cases were due to HDS, respectively.^{24–26} However, in Southeast

Asia, HDS are a more prominent cause of liver injury. In a Korean collaboration among 17 hospitals, 73% of all DILI cases were due to HDS.²⁷ Similarly, a single-hospital study in Singapore reported 71% of liver injury cases were due to HDS. Interestingly, 9 of 31 complementary and alternative medicines identified as causal agents in this study were found to contain adulterants, including pharmaceuticals such as codeine, dexamethasone, and paracetamol.²⁸

The prevalence of liver injury due to HDS relative to medications has also been demonstrated in a retrospective analysis of patients seen in a single Chinese gastroenterology unit, with 40% of the recorded cases being caused by HDS.²⁹ Interestingly, less than 2% of 313 liver injury patients seen in an Indian single center were caused by HDS. The authors speculated that this low frequency was due to both the more common use of HDS after liver injury onset and the health system organization in India, which has a network of specialized medical centers accustomed to, and perhaps less likely to report, the use and adverse events associated with HDS.³⁰

The frequency of liver injury caused by nonprescription performance-enhancing products possibly tainted with or functioning as androgenic anabolic steroids reported both in the DILIN and the Spanish DILI registries is a growing concern. In the DILIN registry, the proportion of cases attributed to HDS increased from 7% in 2004 to 2005 to 20% in 2010 to 2012 and the increase occurred with bodybuilding (2–7%) as well as other HDS (5–12%).³¹ Similarly, in a span of 19 years in the Spanish-DILI Registry, 80% (20/25) of the cases of liver injury due to anabolic steroids occurred in the most recent 3 years of the study (unpublished data).

Among cases of liver injury due to HDS enrolled in prospective registries, 1.5 to 11% have been reported to result in acute liver failure (ALF), underscoring the life-threatening potential of some HDS (►Table 2). Furthermore, HDS, nonprescription medications, weight-loss treatments, and illicit substances were responsible for 10.6% of ALF cases, and ranked second only to antimicrobials as a cause for ALF in the U.S. Acute Liver Failure Study group during a 10-year period.³²

Hepatotoxicity due to HDS is believed to be underdiagnosed. Underreporting probably occurs due to lack of awareness of their hepatotoxic potential and patient reluctance to report use of HDS. Based on a 2007 national health survey, only 43.5% of consumers of HDS disclosed their use to their provider.³³ Besides impeding a correct diagnosis in hepatotoxicity due to HDS, concomitant use of HDS can increase the risk of adverse reaction by interaction with concomitantly used medications.

Clinical Presentation

The liver biochemistry pattern of hepatotoxicity due to HDS can be categorized as hepatocellular, cholestatic, or mixed pattern, similar to the way drug-induced injury is described. However, the hepatocellular pattern of injury seems more frequent than with conventional medications, ranging from 63 to 89% across the prospective registries (►Table 2) and reaching 93% in the ALFSG experience (vs. 77% attributable to

Table 2 Prospective and retrospective studies of drug-induced liver injury. Prevalence and phenotype of hepatotoxicity due to herbal and dietary supplements

		PROSPECTIVE							
		Spanish DILI Registry ²⁵	US DILIN ²⁴	SLATINDILI ²⁶	Korea ²⁷	Singapore ²⁸	US ALF study group ³²	Iceland ²³	
Years		1994–2013	2003–2008	2012–2013	2005–2007	2004–2006	1998–2007	2010–2011	
Type of Registry		National (43 centers)	National (5 centers)	Multinational (9 countries)	National (17 centers)	Single center	National (23 centers)	Population-based study	
DILI cases		861	300	116	371	31	133	96	
Most frequent causative agents n (%)		Antibiotics 332 (38%) Nervous system 128 (15%) Cardiovascular system 98 (11%) Musculo skeletal system 97 (11%)	Antibiotics 136 (45.5%) Central nervous system agents 45 (15%) Dietary supplements 28 (9%)	Antibiotics 31 (27%) Musculo- skeletal system 23 (20%) Nervous system 12 (10%) Genitourinary system and sex hormones 12 (10%)	Herbal medications 102 (27.5%) Health foods or dietary supplements 51 (13.7%) Medicinal herbs or plants 35 (9.4%) Folk remedies 32 (8.6%)	Chinese traditional CAM 17 (55%) Malay CAM 5 (16%) AntiTB drugs 2 (6%)	Antibiotics 61 (46%) CAM, nonprescription medications, dietary supplements, weight-loss treatments, and illicit substances 14 (10.6%) Antiepileptic drugs 11 (8%) Antimetabolites and enzyme inhibitors 11 (8%)	Antibiotics 36 (37%) Dietary supplements 15 (16%) Immunosuppressant drugs 10 (10%) Psychotropic 7 (7%) NSAIDS 6 (6%)	
HDS, n (%)	Total HDS n (%)	54 (6%)	28 (9%)	9 (8%)	271 (73%)	22 (71%)	14 (10.6%)	15 (16%)	
	Mean age (range)	42 (18–78)	45	43 (27–60)	51 (18–79)	–	–	–	
	Herbals	30 (55%)	22 (78%)	5 (55%)	–	0	–	–	
	CAM	4 (7%)	0	–	–	(22 100%)	–	–	
	AAS	20 (37%)	6 (21%)	4 (44%)	–	0	–	–	
	Pattern of injury	–	–	–	–	–	–	–	
	Hepatocellular	42 (78%)	18 (63%)	8 (89%)	211 (78%)	16 (74%)	13 (93%)	7 (47%)	
	Cholestatic /Mixed	12 (22%)	10 (38%)	1 (11%)	60 (22%)	6 (26%)	1 (7%)	8 (53%)	
	DILI with positive autoantibodies	10 (18%)	–	4 (44%)	–	6 (26%)	1 (7%)	–	
	Rechallenge	5 (9.2%)	–	1 (11%)	–	–	–	–	
	Hospitalization	35 (65%)	11 (41%)	4 (44%)	25 (9%)	–	14 (100%)	3 (20%)	
	ALF	3 (5%)	1 (3.5%)	1 (11%)	4 (1.5%)	1 (4.5%)	14 (100%)	0	
	Liver transplant	3 (5%)	1 (3.5%)	0	2 (0.7%)	1 (4.5%)	7 (50%)	0	
	Death	0	0	1 (11%)	2 (0.7%)	0	4 (29%)	0	

Abbreviations: ALF, acute liver failure; AAS, anabolic androgenic steroids; AntiTB, antituberculosis; CAM, complementary and alternative medicine; HDS, herbal and dietary supplements; DILI, drug-induced liver injury.

DILI cases).³² This clinical presentation has prognostic implications, as a hepatocellular pattern has been associated with a more severe outcome.^{34,35} Indeed, need for liver transplantation is more likely in cases with liver injury associated with HDS.³¹

The spectrum of clinical features resulting from hepatotoxicity due to HDS is quite broad. Acute and chronic hepatitis with autoimmune features, hepatic fibrosis, cirrhosis, zonal or diffuse hepatic necrosis, microvesicular steatosis, giant cell hepatitis, cholestatic hepatitis, bile duct injury, veno-occlusive disease, fulminant liver failure, and carcinogenesis have all been described.^{36,37} The autoimmune phenotype may be more common with injury from HDS, occurring in up to 44% of the cases in one series.²⁶ Patients with hepatotoxicity due to HDS tend to be younger than those with hepatotoxicity from conventional medications, probably because younger people more commonly take certain HDS, such as “fat burning,” weight-loss, and body-building agents. No information in pediatric populations is available and may be either under-reported across the registries or there is less use of HDS. Rechallenge, either inadvertent or voluntary, is more common with HDS consumption ranging from 9 to 11% as compared with 6% in an analysis of 520 DILI cases included in the Spanish registry.³⁸

Diagnosis

Making an accurate diagnosis of hepatotoxicity attributable to HDS is predicated upon the same stepwise approach as is followed for conventional drug-related hepatotoxicity, and discussed elsewhere in this issue of *Seminars*. At the outset, the astute clinician must recognize that hepatotoxicity need not present with obvious signs of liver injury such as jaundice or encephalopathy. Rather, liver injury can present in much more subtle ways, such as with malaise, abdominal pain, or nausea. The timing of symptoms with recently begun HDS will suggest a potential causative link. At this earliest stage, however, the clinician must specifically ask about use of HDS, as many may not volunteer this information to their health care providers without prompting.^{15,39–41}

Just as with a DILI diagnosis, making a diagnosis of hepatotoxicity due to HDS requires that other causes, either alternative or pre-existing of liver injury be excluded, including anatomical, infectious, autoimmune, metabolic, ischemic, alcoholic, and inherited processes. Comprehensive serological evaluation and hepatic imaging are used in this process of exclusion.

The respective presentation of liver injury from many pharmaceuticals has been well described in the medical literature. The LiverTox website houses a large number of drugs and descriptions of their respective hepatotoxicity presentations.⁴² Such descriptions help the clinician to establish the association between a hepatotoxic event and the drug with confidence. Unfortunately, there are only a few situations where the phenotype of liver injury due to HDS is so typical that an association between clinical presentation and a product can be made with the same degree of confidence as pharmaceuticals. Anabolic steroidal com-

pounds^{43–46} and other products containing pyrrolidine alkaloids^{47–50} offer one of the few examples where the injury phenotype is stereotypic and many times unmistakable. Only after an exhaustive search for alternative explanations can a diagnosis of liver injury attributable to HDS be made with reasonable confidence.

Even in cases where a methodical evaluation has linked a supplement to an injury event, the vagaries of many natural products preclude an unequivocal causal association to a particular ingredient, or combination of ingredients. For example, the inclusion of an unlabeled ingredient that could lead to harm constitutes adulteration.⁵¹ Adulterants reported include substances such as pharmaceuticals, microbials,^{52,53} heavy metals,^{54–56} and unlabeled botanicals or chemicals. Not infrequently, the adulterant leads to an enhanced desired effect that is in line with the products purported benefit. Sildenafil has been identified in products marketed to enhance sexual performance.^{57,58} Also, herbals may be prone to variability in regards to their ingredients and their respective concentrations^{59–61} due to changes in growth and harvest conditions. Unlabeled botanicals may also show up in HDS. For example, in the DILIN's experience, 40% of HDS that did not list green tea extract (or any of its component catechins) on the label, had catechins found on careful analysis.⁶² Recent work has shown that detecting the genetic sequences of botanicals through barcoding may be of great value to verify ingredients of HDS.⁶³ How such technology can be used to predict or prevent end-organ injury has yet to be determined.

Causality assessment is the systematic or semiquantitative approach to identify an agent as a cause for end-organ injury. This is used commonly in the research setting and for published case reports. Formal assessments were designed with pharmaceuticals in mind and several have been applied to DILI.^{64–67} None were crafted specifically for liver injury from HDS, although experience exists with several approaches.

The Naranjo system has⁶⁸ been used for causality assessment with natural products.⁶⁹ However, it has limited specificity for hepatic reactions. The Roussel Uclaf Causality Assessment Method (RUCAM) was crafted for hepatic adverse reactions from pharmaceuticals,^{64,65,70} and has been used in cases of liver injury induced by HDS quite commonly. The RUCAM assigns points based on the clinical features of a case. However, limitations of this scale when applied to the evaluation of liver injury from HDS have been highlighted. Specifically, an important component of the RUCAM requires an assessment of an agent's labeled reactions, and the literature published about hepatic reactions. Unfortunately, in the case of HDS, the literature is immature and of insufficient quality to fulfill this RUCAM component with confidence in most circumstances.

In another component of the RUCAM, a lower score is awarded in the setting of more than a 90-day period of exposure prior to the onset of injury. However, the inherent variability of botanicals means that different batches of the same product may have different compositions. Hence, latency as a factor in determining the causal association between an agent and liver injury must be thought of

differently with HDS than with pharmaceuticals. Given the lack of verifiable standards in product quality and composition, it is entirely possible, if not probable, that a natural product may vary over time, even if marketed under the same label. Furthermore, causality assessment is confounded by the fact that patients may be taking a single product with single or multiple ingredients, or multiple products concurrently.

The Maria and Victorino Scale represents a modification of the RUCAM.⁶⁶ Its special feature is that it incorporates extrahepatic manifestations of disease that may hint at an autoimmune pathophysiological basis. This score seems to perform less well in causality assessment in most instances of DILI⁷¹ and has not been used to any great extent in the assessment of liver injury due to HDS or pharmaceuticals.

Finally, the expert opinion process represents the standard approach used by the DILIN, including the adjudication of injury due to HDS.⁷² Unlike the above-mentioned scoring systems, the expert opinion approach allows the assessors a greater degree of latitude in making their decisions on causality. Specifically, all clinical details can be taken into account in determining the attribution of liver injury to an agent. Even this approach, however, remains confounded by factors unique to HDS as discussed above.

Given the lack of a causality assessment approach that is perfectly suited to and validated for the nuances of HDS, the DILIN attempted to craft an approach that would perform more reliably in this situation. The process, built upon the expert opinion approach routinely used by the DILIN, puts greater emphasis on the complexity of HDS, the experts' perception of the quality of the available literature and personal experience with injury due to the HDS in question. In a small test-retest reliability study, this approach performed with modest accuracy (weighted kappa statistic 0.53, 95% confidence interval [CI] 0.20–0.86).⁷³ Given this performance, a change in the DILIN's expert opinion approach to causality assessment for HDS was not adopted. However, the challenges remain and merit further study. Until a process that is demonstrably more reliable for liver injury due to HDS is developed, the assessment of causality is best undertaken with the RUCAM or expert opinion process, as has been proposed by others.⁷⁴

Hepatotoxicity due to HDS: Specific Agents, Uses, and Injury Phenotype

– **Table 3** outlines the name, common usages, suggested toxic mechanism, clinical presentation, and liver histology of several HDS linked to hepatotoxicity. The salient features of a chosen few that are more likely to be encountered in clinical practice are discussed in this section as well. The reader is referred to other excellent reviews on hepatotoxicity due to HDS for more details on other products.^{75–77}

As for intended uses, we emphasize that there is no widely accepted classification schema or nomenclature for HDS, many of which are marketed as mixtures of various

ingredients, as opposed to single herbs. In fact, in the DILIN's experience, most products that caused liver injury were proprietary blends, not single herbs. Therefore, in a recent presentation of its data, the DILIN assigned HDS that had been implicated in liver injury to categories based on their purported benefits or main marketed uses (– **Table 4**). This categorization takes into account that many different ingredients often are combined in a given product to achieve a desired effect. Although not a scientific schema, these categories allow clinicians, researchers, and consumers to group HDS for comparison purposes, and to facilitate recognition of clinical presentations that may be common to some HDS. For example, the products generally used for bodybuilding or muscle enhancement lead to an injury that is characteristic, with prolonged jaundice, pruritus, minimal inflammation, and complete recovery. A fundamental problem with any categorization scheme based on purported uses is that some, if not most HDS are marketed for more than one purpose, and are not mutually exclusive.

Ayurvedic Herbs. Traditional medical therapies are commonly used in India for various purposes. These have been linked to both acute and chronic hepatitis. Contamination with heavy metals^{54,56} has been demonstrated. However, whether the contamination was the cause for injury has not been proven.

Androgenic Anabolic Steroids. Liver injury resulting from androgenic anabolic steroids runs the spectrum of space occupying lesions to the more typical cholestatic hepatitis.⁷⁸ Many reports of products used for bodybuilding and muscle enhancement as a suspected cause for liver injury have been published.^{45,46,79,80} Some have been proven to be tainted with anabolic steroids.⁴⁶ Most reported injuries from these products is so typical that the clinical appearance of protracted jaundice in young men taking these agents has become pathognomonic. While the injury is typically cholestatic, the most recent report of hepatotoxicity resulting from performance enhancers suggested that up to a third may be more hepatocellular in nature.⁸¹

Black Cohosh. Commonly used for menopausal symptoms, this product has been named in numerous reports of attributable liver injury,^{82–88} with at least one report of adulteration.⁸⁹ This herb has also been reported to produce an autoimmune-type liver injury.^{86,87} Severe liver injury leading to transplantation also has been reported.^{90–92}

Chaparral. Used for various reasons (e.g., bronchitis, joint pain, weight loss), this herb derived from the creosote bush has been associated with severe liver injury and liver failure.⁹³

Green Tea Extract. Commonly consumed, this agent is often extracted and formed into a more potent substance and is found in many different HDS. Thought to induce oxidative liver injury, several lines of evidence build a convincing case for its hepatotoxic potential. Specifically, toxicity demonstrated in animal studies⁹⁴ and human positive rechallenge cases^{95,96} are most compelling.

Chinese Herbal Remedies. These encompass a wide range of products used for various purposes, with weight loss (Ma-

Table 3 Compendium of herbal and dietary supplements associated with liver injury

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Aloe (<i>Aloe perfoliata</i> var. <i>vera</i> <i>Aloe barbadensis</i> , <i>Aloe arborescens</i>)	Gastrointestinal aliments /topical emollient	Over 75 identified ingredients, including anthraquinones, vitamins, and enzymes. The toxic mechanism is unknown.	Acute HC damage. Female predominance, mean age 58 years. Mean time to onset of symptoms 3 mo. Mean time to resolution 2 mo.	Portal/lobular inflammation with eosinophilic infiltrates and acidophilic bodies	Positive rechallenge ¹²⁴
Androgenic anabolic steroids	Body building	Stanozolol Methylepitiostanol Methasterone The toxic mechanism is unknown.	Male patients, mean age 32 y, mean time to onset 72 d. Mainly HC damage presenting with jaundice (92%) and requiring hospitalization. Patients with high total bilirubin levels at risk of developing acute renal failure. Cases of ALF/ OLTx.	Intrahepatic cholestasis, hepatic steatosis and/or peliosis hepatic Liver tumors (hepatocellular adenoma and carcinoma)	In EU if a "dietary supplement" contains fraudulently substances that are drugs they are considered "illegal drugs" and removed from the market (i.e., EPISTANE and EPISDROL) ¹²⁵
<i>Atractylis gummifera</i> (Distaff thistle, African remedy)	Multiple uses: antipyretic, antiemetic, abortifacient, diuretic, chewing gum	Contains atractyloside and carboxyatractyloside. Inhibition of gluconeogenesis through interference with oxidative phosphorylation. To trigger apoptosis by inducing mitochondrial permeability.	Cases of human poisoning mainly in Africa, resulting in hepatic and renal necrosis Children mean age 9 y. Symptoms appeared few hours after consumption. Most patients developed ALF.	Diffuse hepatic necrosis	¹²⁶
Ayurvedic herbs: (Not all products): <i>Psoralea corylifolia</i> , <i>Acacia catechu</i> , <i>Eclipta alba</i> or <i>Bacopa monnieri</i> , <i>Vetivexia zizanioidis</i>	Miscellaneous purposes. Traditional remedy in India.	Possible contamination with heavy metals (mercury, lead, arsenic)	Acute and chronic hepatitis	Granulomatous hepatitis, cirrhosis	^{54,56}
Bajiaolian (<i>Diosma pleianthum</i>)	Multiple uses: treatment of snake bite, lumbago, dysmenorrhea	Podophyllotoxin	Mainly female, age ranging from 33–56 y. Use of single doses ranging from 12–60 g. Increases in liver tests associated with		¹²⁷

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Black cohosh (<i>Cimicifuga racemosa</i> , <i>Rhizome of Actaea racemosa</i>)	Ameliorating menopausal vasomotor symptoms	Pathophysiological mechanism unknown. Weak inhibitor of CYP 2D6	thrombocytopenia, leucopenia, sensory ataxia, and peripheral numbness. DILL with autoimmune features. Female, mean age 55 y. Symptoms appearing 4 mo after product consumption. Mean time to resolution, 12 wk. The liver damage may range from transient increases in liver enzymes to liver necrosis with ALF.		Associated allergic reactions Safety warnings by HMPc 2010, AEMPS 2006, HMPc 2009. Precaution on use in patients with underlying liver disorders
Boldo leaf extracts Boldo-do-chile (<i>Peumus boldus Molina</i>)	For hepatic and gastrointestinal disorders.	Contains alkaloids, boldine flavonoids, and chenopodium oil. Ascaridole is the toxic ingredient that inhibits oxidative phosphorylation	Mean age 82 y. The symptoms appeared 10 mo after consumption. The liver damage was mainly HC. Mean time to resolution was 1 mo.		130,131
<i>Callilepis laurolea</i> (Impila, Zulu remedy)	Stomach problems, tapeworm infestations, cough, impotence	Attractylosides competitively inhibit the transport of ADP and ATP, blocking mitochondrial oxidative phosphorylation. Cytotoxicity seen in Hep G2 cells by depletion of glutathione.	Cases of acute liver and renal failure. High mortality rate, greater than 90% by 5 d.	Diffuse hepatic necrosis	132
<i>Camellia sinensis</i> , Green tea (Chá verde)	Weight loss	Catechins and their gallic acid esters (Epigallocatechin-3-gallate) induce oxidative stress-liver damage.	Female predominance at younger ages. Presentation mainly as acute HC damage. Immunoallergic autoimmune features generally absent. Latency to onset of symptoms ranging	Inflammatory infiltrates cholestasis, occasional steatosis, and necrosis.	Positive rechallenge Exolise, a hydroalcoholic extract of <i>C. sinensis</i> , has been withdrawn by AEMPS ^{95,96,133}

(Continued)

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Camphor (Cinnamomum camphora)	Rubefacient, mucolytic. Topic and oral administration.	Cyclic terpenes/ ribosome-inactivating proteins. Camphor is metabolized in the liver. Infants are more susceptible for toxicity because of immature hepatic detoxification.	from 10 d to 7 mo. Cases of ALT/OLTx. Acute hepatitis due to accidental exposure to high doses. Two cases, both were infants 2–6 mo. Time to onset between 2–5-d. Resolution after withdrawal. One death.	Acute hepatitis, mimics Reye syndrome. Hepatitis with necrosis	Contraindicated in children under 2 y ^{134,135}
Cascara sagrada (Rhamnus purshiana, cascara buckthorn, Sacred bark)	Constipation	Anthrarcene glycoside Anthraquinones/	Mean age 40 y. Time to onset of symptoms varied from a few days to 2 mo, and the HC damage is typical. The liver injury ranged from mild to severe, but usually resolved rapidly with discontinuation. Severe cases with ALF and development of ascites and portal hypertension have been described.	Cholestatic hepatitis, bile drug injury, portal inflammation, intracanalicular bile stasis, portal bridging fibrosis, mild steatosis	¹²⁶
Cassia angustifolia and Cassia acutifolia (Cassia Senna, Sennosides, senna glycosides)	Constipation	Sennosides are broken down by intestinal bacteria to an active metabolite, rhein anthrone (anthracene glycoside). The hepatotoxicity of rhein involves impairment of mitochondrial function.	Mean age of 78 y. The symptoms appeared 5 mo after consumption. The liver damage was mainly HC. Mean time to resolution was 1 mo.	Portal and lobular cell infiltration, extensive centrilobular necrosis. Canalicular cholestasis	Positive rechallenge ⁹⁵
Centella asiatica	Wound healing and leprosy, and as a psychophysical regenerator and blood purifier	Triterpenoids can produce hepatic injury by promoting apoptosis and altering cell membranes principles.	Mainly women, mean age 54 y. Time to onset ranging from 20–60 d. Mainly HC pattern with autoimmune features (ASMA positive).	Cellular necrosis and apoptosis (eosinophilic degeneration), and lymphoplasmocytic infiltrate.	Positive rechallenge ¹³⁶

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Chaparral (<i>Larrea tridentata</i> , <i>Larrea divaricata</i>) Greasewood or creosote bush	Miscellanea: bronchitis, rheumatic pain, weight loss, stomach pain, liver tonics	Nordihydroguaiaretic acid, is a lignin, which has estrogenic activity, and constitutes up to 10% of dry weight. It is hepatotoxic and a potent inhibitor of cyclooxygenase pathways.	Mean time to resolution 2 months Associated with acute to chronic irreversible liver damage (cirrhosis) with FLF/OLTx Female predominance, age ranging from 25–60 y. Time to onset from 3–52 wk. Resolution time ranged from 1–17 wk.	Cholestatic hepatitis, biliary changes, cirrhosis, massive necrosis	Phytoestrogens may enhance effects of nordihydroguaiaretic acid. ⁹³
Chelidonium majus (<i>Chelidonium majus</i> , Greatercelandine)	Dyspepsia, irritable bowel syndrome; gallstones; abdominal pain	Alkaloids/ dried aerial parts harvested during blossoming	Mainly HC damage with cases of autoimmune features (ANA & ASMA positive); Female preponderance, mean age 50 y (range 37–59 y). Time to onset 28–270 d. Resolution is generally achieved. Case of ALF	Chronic hepatitis, cirrhosis, cholestatic hepatitis, massive necrosis ¹³⁷	Positive rechallenge ¹³⁷
Chinese herbal remedies and teas: Chaso or Onshido	Weight loss	N-nitroso-fenfluramine might be the toxic ingredient. Depletes ATP, impairing mitochondrial oxidative phosphorylation	Mainly Women. Mean age 48 y (range 25–63 y). Time to onset range 5–40 d. Mainly HC and Mixed damage. Mean time to resolution 45 d (range 10–180 d) Also ALF/OLTx and death	Diffuse or massive necrosis with nonspecific inflammatory infiltrate. Ductular proliferation with bile stasis, and bridging fibrosis. ¹³⁸	
Jin Bu Huan (<i>Lycopodium serratum</i>)	Sedation	Levotetrahydroalpine is the active ingredient with structural similarity to pyrrolizidine alkaloids.	Mainly males, mean age 49 y. Time to symptoms onset ranges from 1–52 wk. The time to resolution ranged from 2–30 wk.	Chronic hepatitis, portal and parenchymal lymphocytic inflammation, portal fibrosis, focal necrosis, steatosis, cholestatic hepatitis	
Gran Cao (<i>Glycyrrhiza uralensis</i> ,	Elaboration of candies or sweets. Chronic viral hepatitis.	Glycyrrhizin acid/possible inhibition of NA/K ATPase.	Mainly Male. Mean age 46 y. Mean time to onset 2 mo (range 1–4 mo).	Centrilobular necrosis and fibrosis in cases of prolonged consumption ^{139,140}	

(Continued)

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
<i>Radix Glycyrrhizae</i> Licorice		Triterpenoids promote apoptosis. Other components include flavonoids, isoflavonoids, coumarins.	Mean time to resolution 2 mo. One patient developed ALF/OLT.		
Ma-Huang (<i>Ephedra sinica</i> , <i>Ephedra</i> sp.)	Weight loss	Ephedrine suspected toxic constituent	HC damage with autoimmune features (ANA and ASMA positive), mean age 51 y. Mean time to onset 53 d (range 21–135 d).	Massive necrosis (disproportionate severity for clinical presentation) polymorphonuclear infiltrate	97–99
<i>Polygonum multiflorum</i> He Shou Wu (Heshouwu) and may be an ingredient of various products including Shen Min, Shou Wu Pian and Shou Wu Wan	Premature hair greying, dizziness, constipation	Antraquinones	Mainly males, mean age 48 y (range 24–65 y). Mainly HC damage. Mean time to onset 30 d (range 1–180 d). Cases of ALF/OLTx and death.	Inflammatory cell infiltration, necrosis	141
Skullcap (<i>Scutellaria</i>)	Sedative effect, anti-inflammatory.	Flavonoids and alkylating agents/Toxic metabolites by CYP450. Hepatocyte apoptosis.	Mainly female, age ranging from 28–85 y. Mean time to onset: 3 wk. Acute hepatitis with autoimmune features and cases of ALF/OLT.	Inflammatory infiltrates, bridging fibrosis, cirrhosis. Centrilobular and bridging necrosis.	100
Copalchi (<i>Coutarea latiflora</i> , <i>Hintonia latiflora</i> , <i>Strychnos pseudoquina</i> , <i>Croton niveus</i> , <i>Croton pseudoquina</i>)	Sugar-lowering property (diabetes)	Furanoterpenoids	Acute hepatitis presenting with jaundice. Male predominance, mean age 76 y. Time to onset between 2–13 mo. Resolution in 2–4 mo.	Centrilobular necrosis, lobular inflammatory infiltrate by lymphocytes and eosinophilic cells.	141
Coumarin Mellilot (Sweet clover)	Chronic venous diseases, lymphedema	Coumarin (1,2 benzopyrone) and coumarin derivatives esculetin (6,7-dihydroxycoumarin), scoparone (6,7-dimethoxycoumarin)	Mainly female, mean age 45 y. Mainly HC damage. Acute hepatitis and cases of ALF/OLTx. Heavy consumers of	Chronic hepatitis	Carcinogenic properties. Metabolism through CYP 2A6 ¹⁴²

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Echinacea purpurea (Purple coneflower)	Immunostimulant/wound healing/eczema/psoriasis	Polysaccharides, glycoproteins, caffeic acid derivatives (cichoric acid) and alkaloids. Interaction with cytochrome P450 1A2.	Mainly women. Mean age 60 years Mean time to onset 29-days. Presentation mainly as mixed damage. Mean time to resolution 24-days.	Hepatic necrosis.	Echinacea could interfere with corticosteroid and monoclonal antibody treatment effect. ¹⁴³⁻¹⁴⁵
Flavocoxid (Plant-derived bioflavonoids)	Arthritis or musculoskeletal pain symptoms anti-inflammatory	Contains baicalin and catechins. Dual inhibitor of cyclooxygenase and 5-lypoxigenase enzymes (suggested as alternative to NSAID)	Acute HC injury with immunoallergic manifestations. All women ranging in age from 57-68 y. Time to onset within 1-3 mo; typically presents with jaundice, abdominal pain, fever, and rash. Resolution within 1-3 mo. No ALF or chronic liver injury.	Focal necrosis and inflammation, portal lymphocytic inflammatory infiltrate with some eosinophils and plasma cells	Associated to hypersensitivity reactions ¹⁴⁴
Germander (<i>Teucrium chamaedrys</i> , <i>Teucrium polium</i>) Erva cavalinha in Brazil	Weight loss/tonic	Furan-containing diterpenoids are metabolized via CYP3A4 to electrophilic metabolites that can deplete cellular thiols, increase Ca ²⁺ , and activate Ca ²⁺ -dependent transglutaminase and endonucleases, result in membrane disruption and apoptosis.	Most cases of hepatotoxicity occurred after 2 mo of consumption. The predominant damage was HC. After withdrawal, symptoms generally disappeared within 8 wk. However, cases of fulminant hepatitis, chronic hepatitis, and cirrhosis were also seen.	Acute and chronic hepatitis, cirrhosis, fibrosis, massive necrosis	CYP3A4 induction-mediated increased herbal toxic metabolite ¹⁴⁶
Herbalife Nutritional supplements	Weight reduction/nutritional supplementation/promotion of well-being	Numerous products. Unknown ingredients that may change across countries and over the years. Possible contamination	Female preponderance, mean age 46 y. Latency time to onset range 12-729 d. The damage was predominantly HC in some cases with	Acute and chronic lobular and portal hepatitis, with mixed lobular inflammation (lymphocytic and eosinophilic infiltration),	Positive rechallenge ^{53,101-104}

(Continued)

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Hydroxykut (composition before 2009)	Weight loss, body building	Uncertain. Previous to 2004 mainly <i>Ephedra sinica</i> (Ma-Huang). After 2004, <i>Camellia sinensis</i> . with <i>Bacillus subtilis</i> and <i>cereus</i> .	Autoimmune features. Severity ranged from mild to severe hepatic damage including cirrhosis and ALF requiring liver transplantation. Acute hepatitis. Mean age 31 y (range 17–54 y). Male and HC injury largely. Latency 1–8 wk. Presence of positive ANA & ASMA antibodies. DILI with immune features. Evolution to ALF/OLTx and death.	fibrosis, cirrhosis, hepatic necrosis. Hepatitis with mixed inflammatory infiltrate and cholestasis	FDA Warning in 2009 ^{105,106}
Isabgol (<i>Plantago ovata</i> , <i>Embllica Officialis</i> , <i>Psyllium seed husks</i>)	Constipation	Toxic constituent is unknown.	Female 26 y. HC damage. Resolution within 3 wk. Acute hepatitis.	Giant cell hepatitis. Centrilobular and portal necrosis, lymphocytic infiltrate, bridging and piecemeal necrosis.	Positive rechallenge ⁸
Margosa oil Neem oil (<i>Antelaea azadirachta</i> , <i>Azadirachta indica</i>)	Health tonic, antipyretic, anti-inflammatory	Related to uncoupling of mitochondrial electron transport.	Female infant preponderance, mean age 10 mo, range (1–48 mo). The symptoms appeared 2 h after the consumption. Most patients recovered between 2 d to 4 mo. One patient died.	Reye syndrome, microvesicular steatosis	¹⁴⁷
Mixed preparations Venencapsan	Health tonic, dyspepsia	Prepared from horse chestnut leaf, sweet clover (coumarin), celandine, thistle milk, dandelion root and milfoil. Horse chestnut leaf (<i>Aesculus hippocastanum</i>), sweet clover, and celandine are hepatotoxic.	Female 69 y with HC damage. Time to onset: 6 wk. Resolution in 6 wk.	Portal inflammation, microvesicular steatosis, ballooning, Kupffer cell hyperplasia	Positive rechallenge ¹⁴⁸

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
<i>Morinda citrifolia</i> (Noni juice)	Multiple uses: colds, flu, diabetes, anxiety, and high blood pressure	Anthraquinones	Age ranging from 24–62 y. Symptoms appeared after 1 mo of use. The damage was HC. Mean resolution time was 2 mo (range 0.5–9 mo). Cases of ALF/OLTx.	Hepatic necrosis, ± eosinophilic infiltrates	149
Pennyroyal (<i>Mentha pulegium</i> , <i>Hebeoma pulegoides</i>)	Abortifacient/insect repellent/to induce menses	Pulegone which is metabolized by CYP 450 to Menthofuran/Pulegone depletes hepatic glutathione which increases hepatotoxicity.	Female preponderance, mean age 24 years. Mean time to onset of symptoms 24 hours. Mainly HC damage. Mean time to resolution 1 to 5-days. Cases of ALF and death.	Substantial centrilobular degeneration and massive necrosis.	N-acetylcysteine may be effective in the early phases of poisoning ¹⁴⁷
<i>Piper methysticum</i> (kava kava)	anxiety/depressive symptoms	Kava lactones (kavain, dihydrokavain) metabolized by CYP2D6; intracellular glutathione depletion; Immune-mediated. Kava lactones inhibit cyclooxygenase pathway.	Female preponderance, age range 21 to 81 years. Acute cholestatic hepatitis with jaundice and, less frequently, HC hepatitis. Time to onset of symptoms within 2 to 7 months. Liver damage ranged from transient elevations of liver enzymes to severe and FLF/ OLTx and death.	Cholestatic hepatitis, bile duct injury. Hepatic necrosis.	Genetic deficiency in CYP2D6 may increase the hepatotoxic risk ^{107–113}
Pyrolizidine alkaloids (PA) Herbs rich in PA: <i>Crotalaria</i> sp (Bush tea, Rattlebox) <i>Heliotropium</i> <i>Ilex paraguayensis</i> (Maté) <i>Tu-san-chi</i> (<i>Compositae</i> spp.; Indian Herbs) <i>Senecio</i> spp (Groundsel;	Herbal teas, decoctions or enemas Contamination with toxic weeds)	Pyrolizidine alkaloids/ Toxic metabolites (pyrrole derivatives) that are injurious to sinusoidal endothelium, thus leading to sinusoidal obstruction syndrome [veno-occlusive disease (VOD)]	The acute form typically presents with hepatomegaly and ascites reflecting sinusoidal obstruction. Mortality rates of 20 and 40%. The chronic form of the disease follows a protracted course leading to cirrhosis and portal hypertension	Vascular lesions: veno-occlusive disease. Fibrosis. Cirrhosis.	CYP 3A4 inducers as phenobarbital, can increase toxic pyrroles while CYP 3A4 inhibitors do the opposite. ^{47–50}

(Continued)

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Arnica <i>Tussilago farfara</i> (Colt's foot) <i>Symphytum officinale</i> (Comfrey) <i>Borago officinalis</i> (Borage)		Dose-dependent hepatotoxin			
Rhubarb (<i>Rheum palmatum</i> L., <i>Rheum officinale</i> , Baillon, Rhei radix)	Chronic liver diseases and constipation in Asian countries	Tannins and anthraquinone derivatives (rhein and emodin) Dose dependent effect	Two males infected with HBV, age 45 years. Time to onset of symptoms within 1 to 3 months. ALF/OLTx and death.		139
Sassafras (<i>Sassafras albidum</i> , <i>Sassafras tzumu</i>)	Anticoagulant, antifungal, diaphoretic	Safrol hepatotoxin. Potent inhibitor human CYP1A2, CYP2A6, and CYP2E1.			Hepatic carcinogenesis. Use cautiously in patients taking drugs or herbs metabolized by the cytochrome P450. 150
Saw palmetto Prostata (<i>Serenoa repens</i> , <i>Chamaerops humilis</i> , <i>Sabal Serrulata</i>) Also contains <i>Pygeum africanum</i>	Benign prostatic hyperplasia.	<i>Serenoa repens</i> or <i>serrulata</i> have estrogenic and antiandrogenic effect. <i>Pygeum africanum</i> also has antiandrogenic effect through inhibition of testosterone-5 α -reductase.	Mainly HC damage with autoimmune features in men. Time to onset: 2-wk. Resolution in 3 months.	Chronic hepatitis, fibrosis.	151
Soy isoflavones Soy phytoestrogens (Glycine max)	Ameliorating menopausal symptoms	Most biologically active isoflavones in soy products are genistein, daidzein, equol, and glycitein. Controversial effect due to purported estrogenic activity.	Mainly female. Mean age 47y (range 32–57y). Mean time to onset 5mo (range 1–12 months). Mainly HC damage. Mean time to resolution 4 months (range 3 to 7mo). Mild to moderate increases in transaminases		152
	Abortifacients, heart failure, leprosy, malaria,	Cardiac glycosides: thevetin, peruvoside,	Male, 66 years. Time to onset: 10 days. HC	Centrilobular necrosis.	

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
<i>Thevetia peruviana</i> (Troncomin, Yellow Oleander)	ringworm and indigestion.	nerifolin, thevetoxin and ruvoside/ inactivate the transmembrane Na ⁺ /K ⁺ ATPase pump.	damage with hypersensitivity (rash) and autoimmune features (ANA and ASMA positive).		Withdrawn in Mexico by COFEPRIS ¹⁵³
Usnic acid (<i>Usnea Dasyppoga</i>) LipoKinetic	Weight loss	Usnic acid/ by uncoupling of oxidative phosphorylation in the liver	Mainly HC damage in female. Mean age 27 years (range 20 to 32 years). Mean time to onset 36-days (range 10 to 84-days). Mean time to resolution 71-days (range 28 to 90-days). Cases of ALF/OLTx.	Hepatic necrosis and inflammation	^{116,117}
Valerian (<i>Valeriana officinalis</i>)	Sedative/Insomnia/anxiety/digestive disorders	Alkylating agents	Mainly female. Mean age 47 years. Eventually positive ANA. Symptoms appeared approximately in 1-wk: mainly jaundice dark urine and pale stool. Mean time to resolution: 8 months. Two cases HC and two cases mixed.	Mild hepatitis/ fibrosis/ cirrhosis/	Tablets containing mixed preparations of skullcap or black cohosh and valerian. ¹⁰⁰
<i>Viscum album</i> (Mistletoe)	Asthma, infertility, high blood pressure, dizziness, arthritis.	Mistletoe lectins have strong apoptosis-inducing effects and also stimulate the immune system.	Female 49 years. HC damage. Resolution in 6 wk.	Light inflammatory-cell infiltration of portal tracts with preservation of liver architecture.	Mixed preparation containing motherwort, kelp, wild lettuce, skullcap, and mistletoe. ¹⁵⁴ Positive re-challenge.
Vitamin A Retinol	Immunostimulant, prevention of night blindness.	Dose-dependent toxicity of retinoids on hepatic stellate cells/ portal myofibroblasts, which are the key effector cells in the evolution of fibrosis and cirrhosis.	Hepatic damage depending on the dose and duration of exposure. Mild elevations of serum liver enzymes, cholestatic hepatitis, non-cirrhotic portal hypertension, progressive fibrosis and cirrhosis.	Focal necrosis, sinusoidal lesions, cholestasis, inflammatory infiltrate (round cells, macrophages), and activation and proliferation of stellate cells. Cirrhosis	Liver toxicity rarely occurs, if dose <50,000 IU/day ^{118,119}

(Continued)

Table 3 (Continued)

Herbals & dietary supplements (Botanical names)	Common use	Suspected toxic ingredient/ mechanism toxicity	Phenotype	Liver histology	Comments
Would Sacaca (Croton cajucara Benth) Dragon's Blood (Ama-zonia, Brazil)	Obesity, Hypercholesterolemia	Diterpenoids (similar to Teucrium chamaedrys) are metabolized via CYP3A4 to electrophilic metabolites that can deplete cellular thiols, increase Ca ²⁺ , and activate Ca ²⁺ -dependent transglutaminase and endonucleases, result in apoptosis.	Acute and chronic hepatitis. Cases of ALF/OLTx.		155

Abbreviations: AEMPS, Spanish Medicines Agency and Sanitary Products; ALH, autoimmune hepatitis; ALF, acute liver failure; ANA, antinuclear autoantibodies; ASMA, antismooth muscular antibodies; Chol, cholestatic damage; COFEPRIS, The Federal Commission for the Protection against Sanitary Risk in Mexico; CPMH, Committee on Herbal Medicinal Products; d, days; DLL, drug-induced liver injury; EMA, European Medicines Agency; HC, hepatocellular liver injury; mo, months; NSAID, nonsteroidal anti-inflammatory drugs; OLTx, orthoptic liver transplant; wk, weeks.

Huang, ephedra)⁹⁷⁻⁹⁹ and sedation (Skullcap, Scutellaria)¹⁰⁰ the most often seen. The spectrum of toxicities is wide and includes acute injury with necrosis, to chronic liver disease with cirrhosis.

Herbalife Nutritional Supplements. Many agents fall under this product-line that are used for many reasons. Some have been implicated in liver injury that is suspected to be from bacterial contamination.⁵³ Several other series have described injury attributable to Herbalife products.¹⁰¹⁻¹⁰³ However, a more recent analysis of cases contributed from several countries showed a potential connection between an Herbalife product and liver injury in 16 of 20 cases in which there was sufficient information to perform the RUCAM. It should be noted that many more cases were available for inspection, but with insufficient data to determine causality.¹⁰⁴

Hydroxycut. As in the case of Herbalife, there are many products under this product line label. They are used for many reasons, but primarily for weight loss. Case series^{105,106} of liver injury led to some Hydroxycut products being removed from the market.

Kava. This product has been used as a sedative. Several cases of severe liver injury resulting from Kava have been reported.¹⁰⁷⁻¹¹² Warnings about the use of Kava have been published in the United States and several other countries, and it has been the subject of careful safety reviews.¹¹³

Pyrolizidine Alkaloids. Found in comfrey tea, pyrrolizidine alkaloids induce injury to the sinusoidal epithelium, leading to a Budd-Chiari type picture, with hepatomegaly and ascites. The phenotype is so typical as to be pathognomonic, if in consistent temporal proximity to ingestion of pyrrolizidine alkaloids.

Usnic Acid. Used as an ingredient in weight-loss products, this product is known to uncouple membrane potential and thus induce oxidative stress and cell injury.¹¹⁴ Liver injury cases, including some resulting in liver transplantation, led to removal of some usnic acid containing products from the market.¹¹⁵⁻¹¹⁷

Vitamin A. Known for its dose-dependent hepatotoxicity, the spectrum of injury can range from mild liver test elevations with steatosis, to necrosis.^{118,119} Injury usually occurs after exceeding 50,000 IU per day.

Prevention

Given the current regulatory milieu, the most effective prevention of liver injury due to HDS is awareness among consumers and providers that they have the capacity to cause hepatotoxicity. In addition, health care providers must keep in mind that symptoms associated with liver injury may be protean.

An assessment of whether current regulation is adequate to protect the consumer from injury due to HDS is in order. Preclinical testing would give better assurance of safety. Verification of contents prior to and after marketing would give confidence that product labels accurately reflect contents. On a global scale, the WHO's effort to harmonize regulation and safety standards for herbal medicines should serve as a common platform.¹³

Table 4 The DILIN scheme for categorization of HDS implicated in liver injury

Main marketed purpose for use
Bodybuilding/Muscle Enhancement
Weight Loss
Depression
Sexual Performance
Gastrointestinal Distress
Immune Support
Bone/Joint Support
Chinese Herbs
Miscellaneous

Conclusions and Future Directions

The premise that HDS are safe must be challenged, as there is ample evidence to the contrary. Achieving a culture of safety in the HDS industry will emerge only after the mounting evidence for injury from several HDS is recognized and a new agenda for research and regulation is developed. Such an agenda must take into account the varying regulatory approaches to HDS across the globe, as well as the varying uses as therapeutic agents, performance and appearance enhancers, and as agents to promote well-being.

One of the most pressing needs is for the development of a standard and consistently applied nomenclature for HDS, recognized by all stakeholders, including clinicians, researchers, regulators, and manufacturers. Given the ease of access to HDS, the nomenclature system must be relevant and understandable to the consumer. With a standard system of categorizing HDS, associating injury phenotypes with product types becomes more feasible.

There is also a need to attain a more complete understanding of the epidemiology of liver injury attributable to HDS. Despite numerous reports in the literature, the impact of drug- and dietary supplement-induced hepatotoxicity on public health is unclear, as there are no accurate estimates of the incidence or prevalence of injury. This baseline information ensures that the appropriate resources can be allocated to research, and that regulation is proposed to protect what may be a large segment of the population.

Analysis of product labels reveals their complexity and multiplicity of ingredients. In fact, in the DILIN's experience, a review of listed ingredients revealed that there are more than 20 ingredients in most HDS implicated in liver injury (unpublished data). Identifying the actual ingredient responsible for injury would require a painstaking analytical approach to single out each constituent and perform formal toxicological analysis. A more feasible approach, as the DILIN plans, is to

amass products implicated in liver injury and conduct a frequency analysis for commonly occurring ingredients, or combinations of ingredients. In this way, ingredients can be selected as possibly the cause for injury and subjected to formal toxicology testing.

As it is not required for HDS to undergo preclinical (in vitro and animal) and human clinical testing, such analyses prior to marketing typically are absent. Rather, less rigorous assessments of safety are used to support a product's entry into the market. Hence, product variability, unpredictable pharmacokinetics, interaction among ingredients within a given product, and the effect of HDS on prescribed medications are important concerns. A better understanding of these issues would require detailed and complex chemical analysis followed by formal clinical pharmacology and toxicity testing. To make certain that the findings of such analyses led to safer products, findings would have to be coupled with new regulation which establishes product standards that are then enforced by oversight bodies.

It is likely that voluntary reporting of adverse events from use of HDS is infrequent given the consumer's presumption of safety as well as reluctance to divulge use of HDS to physicians. Hence, measures to promote postmarketing pharmacovigilance are needed. LiverTox,⁴² an authoritative compendium of marketed drugs and their associated liver injuries, will continue to be developed as a resource for liver injury due to HDS. Health care providers must also make use of a voluntary reporting mechanism for suspected cases of hepatotoxicity due to HDS. In the United States and abroad, the FDA's MEDWATCH system (<http://www.fda.gov/Safety/MedWatch/default.htm>) is a valuable tool.

As is the case with several drugs,^{120,121} a genetic basis for injury attributable to some HDS can reasonably be hypothesized. For example, liver injury due to bodybuilding products,^{45,46,78} shown in some reported cases to be tainted with undeclared steroids, leads to a characteristic clinical presentation with prolonged jaundice, initially with hepatocellular injury in some cases,⁸¹ but with evolution to a bland cholestasis, and complete recovery, almost exclusively in young men. Although some of the reproducibility of the injury pattern may result from the demographic of use, commonly being young men, it is also possible that a common genetic mutation or polymorphism in a bile salt transporter may explain such a characteristic picture of injury.

Finally, even with stringent regulation, scrupulous adherence, and vigilant oversight, injury from HDS will occur as it does with conventional medications. Therefore, biomarker development to predict liver injury or predict it at an early stage should be pursued. Biomarkers for liver injury attributable to HDS have been detected with alkaloids and germaneder,^{122,123} providing rationale for additional research in this area.

Acknowledgment

The authors wish to acknowledge Maricruz Vega, MPH, for her expertise in editing and preparing the manuscript.

References

- 1 Navarro VJ. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis* 2009;29(4):373–382
- 2 Commission on Dietary Supplement Labels. Chapter I Dietary Supplement Health And Education Act of 1994. Available at: <http://www.health.gov/dietsupp/ch1.htm>. Accessed January 13, 2014
- 3 Hatch Leads Efforts to Prevent Overregulation of Dietary Supplements. Available at: <http://www.hatch.senate.gov/public/index.cfm/2012/5/hatch-leads-efforts-to-prevent-overregulation-of-dietary-supplements>. Accessed January 13, 2014
- 4 US Food and Drug Administration. Uprizing 2.0: Recall - Undeclared Drug Ingredient: Synthetic Steroid. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm274746.htm>. Accessed January 13, 2014
- 5 US Food and Drug Administration. OxyElite Pro Supplements Recalled. Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm374742.htm>. Accessed January 14, 2014
- 6 US Food and Drug Administration. Medical Foods Guidance Documents & Regulatory Information. Available at: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocuments-RegulatoryInformation/MedicalFoods/default.htm>. Accessed April 9, 2014
- 7 Chalasani N, Vuppalach R, Navarro V, et al. Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: a case series. *Ann Intern Med* 2012;156(12):857–860. W297-300
- 8 European Commission. Herbal Medicinal Products. Available at: http://ec.europa.eu/health/human-use/herbal-medicines/index_en.htm. Accessed January 14, 2014
- 9 European Medicines Agency. Committee on Herbal Medicinal Products (HMPC). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000264.jsp. Accessed January 13, 2014
- 10 European Medicines Agency. Herbal Medicines for Human Use. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_medicines_search_landing_page.jsp&mid=. Accessed January 13, 2014
- 11 Medicines and Healthcare Products Regulatory Agency (MHRA). Herbal Medicines Advisory Committee. Available at: <http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/HerbalMedicinesAdvisoryCommittee/index.htm>. Accessed January 13, 2014
- 12 The WHO Essential Medicines and Health Products Information Portal. Available at: <http://apps.who.int/medicinedocs/en>. Accessed January 13, 2014
- 13 World Health Organization. International Regulatory Cooperation for Herbal Medicines (IRCH). Available at: <http://www.who.int/medicines/areas/traditional/irch/en/>. Accessed January 13, 2014
- 14 World Health Organization. General Information on IRCH. Available at: <http://www.who.int/medicines/areas/traditional/geninfo/en/>. Accessed January 13, 2014
- 15 Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med* 1993; 328(4):246–252
- 16 Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003–2006. *J Nutr* 2011;141(2):261–266
- 17 Picciano MF, Dwyer JT, Radimer KL, et al. Dietary supplement use among infants, children, and adolescents in the United States, 1999–2002. *Arch Pediatr Adolesc Med* 2007;161(10):978–985
- 18 Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med* 2013;173(5): 355–361
- 19 World Health Organization. WHO traditional medicine strategy 2002–2005. Geneva: WHO; 2002
- 20 Skeie G, Braaten T, Hjartaker A, et al. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. *Eur J Clin Nutr* 2009;63(Suppl 4): S226–S238
- 21 Lindstrom A, Ooyen C, Lynch ME, Blumenthal M. Herb supplement sales increase 5.5% in 2012: herbal supplement sales rise for 9th consecutive year. *Herbal Gram* 2013;99:60–65
- 22 PRWeb Focus. Global Herbal Supplements and Remedies Market to Reach US\$107 Billion by 2017, According to New Report by Global Industry Analysts, Inc. Available at: http://www.prweb.com/releases/herbal_supplements/herbal_remedies/prweb9260421.htm. Accessed January 13, 2014
- 23 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(7):1419–1425, e1–e3, quiz e19–e20
- 24 Chalasani N, Fontana RJ, Bonkovsky HL, et al; 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(6):1924–1934, e1–e4
- 25 Medina-Cáliz I, González-Jiménez A, Bessone F, et al. Variations in drug-induced liver injury (DILI) between different prospective DILI registries. *Clin Ther* 2013;35(8 Suppl): S24
- 26 Bessone F, Hernandez N, Sanchez A, et al. The Spanish–Latin American DILI Network: preliminary results from a collaborative strategic initiative. *J Hepatol* 2013;58(Suppl 1):212–213
- 27 Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol* 2012; 107(9):1380–1387
- 28 Wai CT, Tan BH, Chan CL, et al. Drug-induced liver injury at an Asian center: a prospective study. *Liver Int* 2007;27(4):465–474
- 29 Wang YP, Shi B, Chen YX, Xu J, Jiang CF, Xie WF. Drug-induced liver disease: an 8-year study of patients from one gastroenterological department. *J Dig Dis* 2009;10(3):195–200
- 30 Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010;105(11):2396–2404
- 31 Navarro VJ, Barnhart HX, Bonkovsky HL, et al. The rising burden of herbal and dietary supplement induced hepatotoxicity in the U.S. A. Abstract presented at: 64th Annual Meeting of the American Association for the Study of Liver Diseases. ; November 1–5, 2013; Washington, DC
- 32 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(6):2065–2076
- 33 Wu CH, Wang CC, Kennedy J. Changes in herb and dietary supplement use in the U.S. adult population: a comparison of the 2002 and 2007 National Health Interview Surveys. *Clin Ther* 2011;33(11):1749–1758
- 34 Andrade RJ, Lucena MI, Fernández MC, 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(2): 512–521
- 35 Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology* 2005;42(2):481–489
- 36 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(8):1018–1023
- 37 Estes JD, Stolpman D, Olyaei A, et al. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg* 2003;138(8):852–858
- 38 Fernández-Castañer A, García-Cortés M, Lucena MI, et al. [An analysis of the causes, characteristics, and consequences of reexposure to a drug or compound responsible for a hepatotoxicity event]. *Rev Esp Enferm Dig* 2008;100(5):278–284

- 39 Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE. Americans' views on the use and regulation of dietary supplements. *Arch Intern Med* 2001;161(6):805-810
- 40 Robinson A, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med* 2004;12(2-3):90-98
- 41 Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;280(18):1569-1575
- 42 LiverTox® Clinical and Research Information on Drug Induced Liver Injury. Available at: <http://livertox.nih.gov/>. Accessed January 13, 2014
- 43 Isharkawy AM, McPherson S, Masson S, et al. Cholestasis secondary to anabolic steroid use in young men. *BMJ* 2012;344:468
- 44 Turani H, Levi J, Zevin D, Kessler E. Hepatic lesions in patients on anabolic androgenic therapy. *Isr J Med Sci* 1983;19(4):332-337
- 45 Timcheh-Hariri A, Balali-Mood M, Aryan E, Sadeghi M, Riahi-Zanjani B. Toxic hepatitis in a group of 20 male body-builders taking dietary supplements. *Food Chem Toxicol* 2012;50(10):3826-3832
- 46 Singh V, Rudraraju M, Carey EJ, et al. Severe hepatotoxicity caused by a methasteron-containing performance-enhancing supplement. *J Clin Gastroenterol* 2009;43(3):287
- 47 Tandon BN, Tandon HD, Tandon RK, Narndranathan M, Joshi YK. An epidemic of veno-occlusive disease of liver in central India. *Lancet* 1976;2(7980):271-272
- 48 Weston CFM, Cooper BT, Davies JD, Levine DF. Veno-occlusive disease of the liver secondary to ingestion of comfrey. *Br Med J (Clin Res Ed)* 1987;295(6591):183
- 49 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
- 50 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):349-352
- 51 US Food and Drug Administration. Federal Food, Drug, and Cosmetic Act (FD&C Act). Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/default.htm>. Accessed January 13, 2014
- 52 Kneifel W, Czech E, Kopp B. Microbial contamination of medicinal plants—a review. *Planta Med* 2002;68(1):5-15
- 53 Stickel F, Droz S, Patsenker E, et al. Severe hepatotoxicity following ingestion of Herbalife contaminated with *Bacillus subtilis*. *J Hepatol* 2009;50:111-117
- 54 Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. *JAMA* 2008;300(8):915-923
- 55 Wong MK, Tan P, Wee YC. Heavy metals in some Chinese herbal plants. *Biol Trace Elem Res* 1993;36(2):135-142
- 56 Ernst E. Heavy metals in traditional Indian remedies. *Eur J Clin Pharmacol* 2002;57(12):891-896
- 57 Miller GM, Stripp R. A study of western pharmaceuticals contained within samples of Chinese herbal/patent medicines collected from New York City's Chinatown. *Leg Med (Tokyo)* 2007;9(5):258-264
- 58 Fleshner N, Harvey M, Adomat H, et al. Evidence for contamination of herbal erectile dysfunction products with phosphodiesterase type 5 inhibitors. *J Urol* 2005;174(2):636-641, discussion 641, quiz 801
- 59 Komes D, Belščak-Cvitanović A, Horžić D, Rusak G, Likić S, Berendika M. Phenolic composition and antioxidant properties of some traditionally used medicinal plants affected by the extraction time and hydrolysis. *Phytochem Anal* 2011;22(2):172-180
- 60 Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in commercial ginseng products: an analysis of 25 preparations. *Am J Clin Nutr* 2001;73(6):1101-1106
- 61 Ye F, Wang H, Jiang S, et al. Quality evaluation of commercial extracts of *Scutellaria baicalensis*. *Nutr Cancer* 2004;49(2):217-222
- 62 Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. *Dig Dis Sci* 2013;58(9):2682-2690
- 63 Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DINA barcoding detects contamination and substitution in North American herbal products. *BMC Med* 2013;11:2-13
- 64 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):1323-1330
- 65 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):1331-1336
- 66 Maria VAJ, Victorino RMM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997;26(3):664-669
- 67 Aithal GP, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol* 2000;33(6):949-952
- 68 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-245
- 69 Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts : a systematic review by the US Pharmacopeia. *Drug Saf* 2008;31(6):469-484
- 70 Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990;11(2):272-276
- 71 Lucena MI, Camargo R, Andrade RJ, Pérez-Sánchez CJ, Sánchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology* 2001;33(1):123-130
- 72 Fontana RJ, Watkins PB, Bonkovsky HL, et al. Rationale, design and conduct of the Drug Induced Liver Injury Network prospective study. *Drug Saf* 2009;32:55-68
- 73 Navarro VJ, Barnhart HX, Bonkovsky HL, et al. Diagnosing hepatotoxicity attributable to herbal and dietary supplements: test-retest reliability of novel causality assessment tool. *J Hepatol* 2012;55(Suppl 2):S536
- 74 Teschke R, Schwarzenboeck A, Eickhoff A, Frenzel C, Wolff A, Schulze J. Clinical and causality assessment in herbal hepatotoxicity. *Expert Opin Drug Saf* 2013;12(3):339-366
- 75 Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. *Liver Int* 2011;31(5):595-605
- 76 Strader DB, Navarro VJ, Seeff LB. Hepatotoxicity of herbal preparations. In: Boyer TD, Manns MP, Sanyal AJ, eds. *Zakim and Boyer's Hepatology: A Textbook of Liver Disease*. 6th ed. Philadelphia, PA: Saunders; 2012:462-475
- 77 Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther* 2013;37(1):3-17
- 78 Ishak KG. Hepatic lesions caused by anabolic and contraceptive steroids. *Semin Liver Dis* 1981;1(2):116-128
- 79 Haupt HA, Rovere GD. Anabolic steroids: a review of the literature. *Am J Sports Med* 1984;12(6):469-484
- 80 DesJardins M. Supplement use in the adolescent athlete. *Curr Sports Med Rep* 2002;1(6):369-373
- 81 Martin DJ, Partridge BJ, Shields W. Hepatotoxicity associated with the dietary supplement N.O.-XPLode. *Ann Intern Med* 2013;159(7):503-504
- 82 Vitetta I, Thomsen M, Sali A. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2003;214:411-412

- 83 Nisbet BC, O'Connor RE. Black cohosh-induced hepatitis. *Del Med J* 2007;79(11):441-444
- 84 Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2002;177(8):440-443
- 85 Vannacci A, Lapi F, Gallo E, et al. A case of hepatitis associated with long-term use of *Cimicifuga racemosa*. *Altern Ther Health Med* 2009;15(3):62-63
- 86 Pierard S, Coche JC, Lanthier P, et al. Severe hepatitis associated with the use of black cohosh: a report of two cases and an advice for caution. *Eur J Gastroenterol Hepatol* 2009;21(8):941-945
- 87 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):575-577
- 88 Mahady GB, Low Dog T, Barrett ML, et al. United States pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008;15:628-638
- 89 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):268-275
- 90 Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med J Aust* 2003;179(7):390-391
- 91 Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. *Dig Dis Sci* 2005;50(3):538-539
- 92 Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl* 2006;12(6):989-992
- 93 Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. *Arch Intern Med* 1997;157(8):913-919
- 94 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):409-416
- 95 García-Cortés M, Borraz Y, Lucena MI, 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(11):688-695
- 96 Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann Intern Med* 2006;144(1):68-71
- 97 Skoulidis F, Alexander GJM, Davies SE. Ma huang associated acute liver failure requiring liver transplantation. *Eur J Gastroenterol Hepatol* 2005;17(5):581-584
- 98 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):1062-1064
- 99 Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. *Am J Gastroenterol* 1996;91(7):1436-1438
- 100 MacGregor FB, Abernethy VE, Dahabra S, Cobden I, Hayes PC. Hepatotoxicity of herbal remedies. *BMJ* 1989;299(6708):1156-1157
- 101 Elinav E, Pinsky G, Safadi R, et al. Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007;47(4):514-520
- 102 Schoepfer AM, Engel A, Fattinger K, et al. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol* 2007;47(4):521-526
- 103 Manso G, López-Rivas L, Salgueiro ME, et al. Continuous reporting of new cases in Spain supports the relationship between Herbalife® products and liver injury. *Pharmacoepidemiol Drug Saf* 2011;20(10):1080-1087
- 104 Haleboua-De Marzio D, Vega M, Schifter-Weber J, et al. An International Effort to Assess Hepatotoxicity Associated with Some Herbalife® Products. *Hepatology* 2013;58(Suppl 1):383
- 105 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
- 106 Fong TL, Klontz KC, Canas-Coto A, et al. Hepatotoxicity due to hydroxycut: a case series. *Am J Gastroenterol* 2010;105(7):1561-1566
- 107 Strahl S, Ehret V, Dahm HH, Maier KP. [Necrotizing hepatitis after taking herbal remedies]. *Dtsch Med Wochenschr* 1998;123(47):1410-1414
- 108 Escher M, Desmeules J, Giostra E, Mentha G. Hepatitis associated with Kava, a herbal remedy for anxiety. *BMJ* 2001;322(7279):139
- 109 Bujanda L, Palacios A, Silvariño R, Sánchez A, Muñoz C. [Kava-induced acute icteric hepatitis]. *Gastroenterol Hepatol* 2002;25(6):434-435
- 110 Stickel F, Baumüller HM, Seitz K, et al. Hepatitis induced by Kava (*Piper methysticum* rhizoma). *J Hepatol* 2003;39(1):62-67
- 111 Kraft M, Spahn TW, Menzel J, et al. [Fulminant liver failure after administration of the herbal antidepressant Kava-Kava]. *Dtsch Med Wochenschr* 2001;126(36):970-972
- 112 Thomsen M, Vitetta L, Schmidt M, Sali A. Fatal fulminant hepatic failure induced by a natural therapy containing kava. *Med J Aust* 2004;180(4):198-199, author reply 199
- 113 Ulbricht C, Basch E, Boon H, et al. Safety review of kava (*Piper methysticum*) by the Natural Standard Research Collaboration. *Expert Opin Drug Saf* 2005;4(4):779-794
- 114 Han D, Matsumaru K, Rettori D, Kaplowitz N. Usnic acid-induced necrosis of cultured mouse hepatocytes: inhibition of mitochondrial function and oxidative stress. *Biochem Pharmacol* 2004;67(3):439-451
- 115 Durazo FA, Lassman C, Han SH, et al. Fulminant liver failure due to usnic acid for weight loss. *Am J Gastroenterol* 2004;99(5):950-952
- 116 Favreau JT, Ryu ML, Braunstein G, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med* 2002;136(8):590-595
- 117 Yellapu RK, Mittal V, Grewal P, Fiel M, Schiano T. Acute liver failure caused by 'fat burners' and dietary supplements: a case report and literature review. *Can J Gastroenterol* 2011;25(3):157-160
- 118 Fallon MB, Boyer JL. Hepatic toxicity of vitamin A and synthetic retinoids. *J Gastroenterol Hepatol* 1990;5(3):334-342
- 119 Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology* 1991;100(6):1701-1709
- 120 Lucena MI, Molokhia M, Shen Y, et al; Spanish DILI Registry; EUDRAGENE; DILIN; DILIGEN; International SAEC. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology* 2011;141(1):338-347
- 121 Daly AK, Donaldson PT, Bhatnagar P, et al; DILIGEN Study; International SAE Consortium. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet* 2009;41(7):816-819
- 122 Lin G, Wang JY, Li N, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of *Gynura segetum*. *J Hepatol* 2011;54(4):666-673
- 123 De Berardinis V, Moulis C, Maurice M, et al. Human microsomal epoxide hydrolase is the target of germander-induced autoantibodies on the surface of human hepatocytes. *Mol Pharmacol* 2000;58(3):542-551
- 124 Yang HN, Kim DJ, Kim YM, et al. Aloe-induced toxic hepatitis. *J Korean Med Sci* 2010;25(3):492-495
- 125 AEMPS. Retirada de los productos episdro y epistane. In: SANITARIOS AAEDMYP ed. Ministerio de sanidad, servicios sociales e igualdad; 2013. Available at: http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/med-Illegales/2013/docs/ICM_MI_09-2013-episdro-epistane.pdf. Accessed January 14, 2014

- 126 Nadir A, Reddy D, Van Thiel DH. Cascara sagrada-induced intrahepatic cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity. *Am J Gastroenterol* 2000;95(12):3634–3637
- 127 Kao WF, Hung DZ, Tsai WJ, Lin KP, Deng JF. Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. *Hum Exp Toxicol* 1992;11(6):480–487
- 128 European Medicines Agency. Assessment Report on *Cimicifuga racemosa* (L.) Nutt. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/05/WC500106358.pdf. Accessed January 14, 2014
- 129 de Sanidad M, Sociales e Igualdad S. AEMPS. Extracto de la raíz de “*Cimicifuga racemosa*” y lesiones hepáticas. Available at: http://www.aemps.gob.es/informa/notasInformativas/medicamento-sUsoHumano/seguridad/2006/docs/NI_2006-06_cimicifuga.pdf. Accessed January 14, 2014
- 130 European Medicines Agency. Assessment report on *Peumus boldus* Molina, folium. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2009/12/WC500018102.pdf. Accessed January 14, 2014
- 131 Piscaglia F, Leoni S, Venturi A, Graziella F, Donati G, Bolondi L. Caution in the use of boldo in herbal laxatives: a case of hepatotoxicity. *Scand J Gastroenterol* 2005;40(2):236–239
- 132 Sohni YR. The toxicity of *Callilepis laureola*, a South African traditional herbal medicine. *Clin Biochem* 2002;35(6):499
- 133 AEMPS. Suspensión de comercialización de la especialidad farmacéutica Exolise®: Extracto etanólico de *camelia sinensis* (te verde). Available at: http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2003/NI_2003-03_exolise.htm. Accessed January 13, 2014
- 134 Jimenez JF, Brown AL, Arnold WC, Byrne WJ. Chronic camphor ingestion mimicking Reye’s syndrome. *Gastroenterology* 1983;84(2):394–398
- 135 Uc A, Bishop WP, Sanders KD. Camphor hepatotoxicity. *South Med J* 2000;93(6):596–598
- 136 Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of *Centella asiatica*. *Rev Esp Enferm Dig* 2005;97(2):115–124
- 137 Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Gastroenterology* 1999;117(5):1234–1237
- 138 Adachi M, Saito H, Kobayashi H, et al. Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. *Ann Intern Med* 2003;139(6):488–492
- 139 Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. *Aliment Pharmacol Ther* 2006;24(8):1179–1186
- 140 Shah M, Williams C, Aggarwal A, Choudhry WM. Licorice-related rhabdomyolysis: a big price for a sweet tooth. *Clin Nephrol* 2012;77(6):491–495
- 141 Bruguera M, Herrera S, Lázaro E, Madurga M, Navarro M, de Abajo FJ. [Acute hepatitis associated with Colpachi intake. Apropos of 5 cases]. *Gastroenterol Hepatol* 2007;30(2):66–68
- 142 Abraham K, Wöhrln F, Lindtner O, Heinemeyer G, Lampen A. Toxicology and risk assessment of coumarin: focus on human data. *Mol Nutr Food Res* 2010;54(2):228–239
- 143 Hernández S, di Pace F, Bessone M, et al. Espectro de la Hepatotoxicidad en Latinoamérica: Fundación y Resultados iniciales del Registro Español-. Latinoamericano de Hepatotoxicidad. *Gastroenterol Hepatol* 2013;36(Suppl 1):27–97
- 144 Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. *Pharmacoevidemol Drug Saf* 2009;18(11):1039–1047
- 145 Werneke U, Earl J, Seydel C, Horn O, Crichton P, Fannon D. Potential health risks of complementary alternative medicines in cancer patients. *Br J Cancer* 2004;90(2):408–413
- 146 Gori L, Galluzzi P, Mascherini V, et al. Two contemporary cases of hepatitis associated with *Teucrium chamaedrys* L. decoction use: case reports and review of literature. *Basic Clin Pharmacol Toxicol* 2011;109(6):521–526
- 147 Anderson IB, Mullen WH, Meeker JE, et al. Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. *Ann Intern Med* 1996;124(8):726–734
- 148 De Smet PA, Van den Eertwegh AJ, Lesterhuis W, Stricker BH. Hepatotoxicity associated with herbal tablets. *BMJ* 1996;313(7049):92
- 149 Stadlbauer V, Weiss S, Payer F, Stauber RE. Herbal does not at all mean innocuous: the sixth case of hepatotoxicity associated with morinda citrifolia (noni). *Am J Gastroenterol* 2008;103(9):2406–2407
- 150 Ueng YF, Hsieh CH, Don MJ. Inhibition of human cytochrome P450 enzymes by the natural hepatotoxin safrole. *Food Chem Toxicol* 2005;43(5):707–712
- 151 Hamid S, Rojter S, Vierling J. Protracted cholestatic hepatitis after the use of prostata. *Ann Intern Med* 1997;127(2):169–170
- 152 Wiwanitkit V. Excessive consumption of soybean milk and unexplained hepatitis. *J Postgrad Med* 2012;58(3):226–227
- 153 Secretaria de Salud de Mexico. COFEPRIS. Comunicado a los consumidores del producto CAPSLIM. Available at: <http://www.cofepris.gob.mx/AZ/Documents/COMUNICADOCAPSLIM.pdf>. Accessed January 14, 2014
- 154 Harvey J, Colin-Jones DG. Mistletoe hepatitis. *Br Med J (Clin Res Ed)* 1981;282(6259):186–187
- 155 Soares MdoC. Would *Sacaca*, *Croton cajucara* Benth (Euphorbiaceae) be an hepatotoxic plant like *Germander*, *Teucrium chamaedrys* L. (Labiatae)? *Rev Soc Bras Med Trop* 2004;37(Suppl 2):96–97