Clinical Gastroenterology and Hepatology 2018;16:1495–1502

Herbal and Dietary Supplement-Induced Liver Injuries in the Spanish DILI Registry

Inmaculada Medina-Caliz,[*] Miren Garcia-Cortes,[*] Andres Gonzalez-Jimenez,[*] Maria R. Cabello,[*] Mercedes Robles-Diaz,[*] Judith Sanabria-Cabrera,[*,‡] Rocio Sanjuan-Jimenez,[*,‡] Aida Ortega-Alonso,[*] Beatriz García-Muñoz,[*] Inmaculada Moreno,[*] Miguel Jimenez-Perez,[§] M Carmen Fernandez,[‖] Pere Ginés,[¶] Martin Prieto,[#] Isabel Conde,[#] Hacibe Hallal,[**] German Soriano,[‡‡] Eva Roman,[‡‡] Agustin Castiella,[§§] Encarnacion Blanco-Reina,[*] Maria R. Montes,[*] Marta Quiros-Cano,[*] Flores Martin-Reyes,[*] M. Isabel Lucena,[*,‡] and Raul J. Andrade,[*] on behalf of the Spanish DILI Registry

*Unidad de Gestión Clínica de Aparato Digestivo, Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain; ‡UICEC Instituto de Investigación Biomédica de Málaga, Plataforma SCReN (Spanish Clinical Research Network), Servicio de Farmacología Clínica, Hospital Universitario Virgen de la Victoria, Málaga, Spain; §Unidad de Gestión Clínica de Aparato Digestivo, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Regional de Málaga, Málaga, Spain; ‖Servicio de Farmacia, Hospital de Torrecardenas, Almeria, Spain; ¶Liver Unit, Hospital Clínic, University of Barcelona, Institut d'Investigaciones Biomèdiques August Pi Sunyer, CIBERehd, Barcelona, Spain; #Unidad de Gestión Clínica de Enfermedades Digestivas, IISLaFe, Hospital La Fe, CIBERehd, Valencia, Spain; **Servicio de Aparato Digestivo, Hospital Morales Meseguer, Murcia, Spain; ‡‡Servicio de Aparato Digestivo, Hospital de la Santa Creu i Sant Pau, CIBERehd, Barcelona, Spain; §§Servicio de Aparato Digestivo, Hospital de Mendaro, Gipuzkoa, Spain*

BACKGROUND & AIMS: **There have been increasing reports of liver injury associated with use of herbal and dietary supplements, likely due to easy access to these products and beliefs among consumers that they are safer or more effective than conventional medications. We aimed to evaluate clinical features and outcomes of patients with herbal and dietary supplement-induced liver injuries included in the Spanish DILI Registry.**

METHODS: **We collected and analyzed data on demographic and clinical features, along with biochemical parameters, of 32 patients with herbal and dietary supplement-associated liver injury reported to the Spanish DILI registry from 1994 through 2016. We used analysis of variance to compare these data with those from cases of liver injury induced by conventional drugs or anabolic androgenic steroid-containing products.**

RESULTS: **Herbal and dietary supplements were responsible for 4% (32 cases) of the 856 DILI cases in the registry; 20 cases of DILI (2%) were caused by anabolic androgenic steroids. Patients with herbal and dietary supplement-induced liver injury were a mean age of 48 years and 63% were female; they presented a mean level of alanine aminotransferase 37-fold the upper limit of normal, 28% had hypersensitivity features, and 78% had jaundice. Herbal and dietary supplement-induced liver injury progressed to acute liver failure in 6% of patients, compared with none of the cases of anabolic androgenic steroid-induced injury and 4% of cases of conventional drugs. Liver injury after repeat exposure to the same product that caused the first DILI episode occurred in 9% of patients with herbal and dietary supplement-induced liver injury vs none of the patients with anabolic androgenic steroid-induced injury and 6% of patients with liver injury from conventional drugs.**

Abbreviations used in this paper: AAS, anabolic androgenic steroids; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CAM, complementary and alternative medicine; CIOMS, Council for International Organizations of Medical Sciences; DILI, drug-induced liver injury; GGT, gamma-glutamyl transpeptidase; HDS, herbal and dietary supplements; HILI, herbal and dietary supplement–induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2017.12.051

CONCLUSION: **In an analysis of cases of herbal and dietary supplement-induced liver injury in Spain, we found cases to be more frequent among young women than older patients or men, and to associate with hepatocellular injury and high levels of transaminases. Herbal and dietary supplement-induced liver injury is more severe than other types of DILI and re-exposure is more likely. Increasing awareness of the hepatoxic effects of herbal and dietary supplements could help physicians make earlier diagnoses and reduce the risk of serious liver damage.**

Keywords: Hepatotoxicity; Clinical Presentation; Herbal Signature; Re-challenge.

Herbal medicinal products are medicinal products where the active ingredient consists exclusively of single herbal substances or a combination of them. Nowadays, the term *herb-containing products* is widely used and may comprise both herbal medicinal products and traditional herbal medicinal products as well as herbal formulations manufactured to be used as dietary supplements. The classification and regulation of such products are heterogeneous and vary between different countries. In the European Union, the first 2 categories mentioned previously are classified as herbal medicinal products, which must fulfill requirements for efficacy, safety, and quality standards.[1,2] On the other hand, some herb-containing products are manufactured as herbal and dietary supplements (HDS) from which most of the problems stem if they are contaminated or adulterated with undeclared botanical or pharmaceutical ingredients.[2] In the United States, the Dietary Supplement Health and Education Act defines a dietary supplement as any product intended to supplement, but not substitute for, the diet.[3]

The real prevalence of HDS consumption is unknown. Surveys found an estimated weighted overall plant food supplement usage prevalence rate ranging from 18.8%[4] in European countries to approximately 50% usage in the United States, a dramatic rise.[5] The apparent increase in consumption of these products in Western countries, is believed to stem from the widespread opinion that herbal dietary supplements are safe due to their "natural" origin, together with their easier purchasing, and has favored the increase in liver injury recognition due to HDS products.[6]

In many countries HDS are classified differently from conventional pharmaceutical products,[7] and as such escape regulations applied to the latter group in terms of efficacy and safety testing.[8] Although there is considerable evidence supporting health benefits of herb-containing products, they are not exempt of adverse events including liver damage. In a population-based study in Iceland, 16% of drug-induced liver injury (DILI) cases were attributed to use of HDS, with a total annual DILI incidence rate of 19.1 cases per 100,000 habitants.[9] The DILIN has reported increases in HDS-induced liver injury (HILI) from 7% to 20% between 2004 and 2013.[7]

The proportion of HILI cases included in drug-induced liver injury registries or in large DILI cohorts varies widely among countries, with figures ranging from 1.3 to 73%.[10–18] Several studies have also observed elevated transplantation rates in DILI cases induced by complementary and alternative medicine (CAM).[7,19] Goldberg et al[20] found that the incidence of drug-induced acute liver failure (ALF) was 1.61 per million person-years in adults, and HDS were implicated in 18% of cases.

The aim of this study was to analyze a series of HILI cases in the Spanish DILI registry and compare them with DILI cases related to conventional medication and anabolic androgenic steroids (AAS), so to define the clinical phenotype and outcome of HILI in Spain.

Patients and Methods

All HILI cases reported to the Spanish DILI registry between 1994 and 2016 were included in this study. Demographics, clinical and biochemical parameters of these cases were analyzed and compared with DILI cases due to conventional drugs and AAS in the same registry. Cases caused by illicit AAS (AAS hepatotoxicity) were considered separately from HILI cases due to their distinct phenotype, which has been previously reported.[21] In patients with more than 1 DILI episode, only 1 episode was included in the analysis, always the episode with most available information The operational structure of the registry, data recording and case ascertainment have been reported elsewhere.[14] A structured protocol was used for data collection with the following information: (1) compatible temporal relationship between drug intake and appearance of liver disease; (2) serology biochemical, imaging and histological data to exclude alternative liver diseases; and (3) outcome of liver damage.

The biochemical criteria for DILI were initially the consensus criteria reported by the Council for International Organization of Medical Sciences (CIOMS), and in 2011 adapted to those of Aithal et al (alanine transaminase [ALT] $\geq 5\times$ the upper limit of normal [ULN], alkaline phosphatase [ALP] $\geq 2\times$ ULN or ALT $\geq 3\times$ ULN + total bilirubin $\geq 2\times$ ULN).[22,23] The pattern of liver injury was classified based on R values (ALT/ULN)/(ALP/ULN) calculated from the first available blood test after DILI recognition. DILI cases were classified as mild, moderate, severe or fatal based on the DILI severity clasification.[23] Hypersensitivity referred to the presence of any of the following features during the DILI episode:

fever, rash, serum eosinophilia (eosinophils >4%), lymphopenia (lymphocytes <10%) or arthralgia. The CIOMS/Roussel Uclaf Causality Assessment Method (RUCAM) scale was applied to all cases that were diagnosed as DILI by a panel of experts.[24]

This study was approved by the local Ethics Committee of the coordinating center at the Virgen de la Victoria University Hospital in Málaga, Spain. All subjects gave informed written consent.

Statistical Analyses

Variables were examined using descriptive statistics. Analysis of variance was used for comparisons of more than 2 groups. Where variables did not follow a normal distribution, nonparametric analyses (Kruskal-Wallis test) were used. Post-hoc pairwise comparisons were performed using the Fisher's least significant difference method. Differences were reported as statistically significant if the P value was <.05. Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY).

Results

Of a total of 856 hepatotoxicity cases recorded in the Spanish DILI registry between the years 1994 and 2016, 32 cases were related to HDS products. This corresponded to 3.7% of the total number of cases, and HDS represented the sixth-highest category in terms of case frequency, behind anti-infectives (37%), nervous system (14%), musculoskeletal system (11%), cardiovascular system (11%), and antineoplastic drugs (8%). An additional, 20 cases (2.3%) were induced by AAS products and the remaining 804 cases were induced by conventional medication. The temporal trend of HILI, DILI, and AAS hepatotoxicity in the Spanish DILI registry is depicted in Figure 1. The number of HILI cases increased steadily up to 2013 and remained constant thereafter, ranging from 2% to 6%, with the majority of causative HDS being multi-ingredient products in 2016.

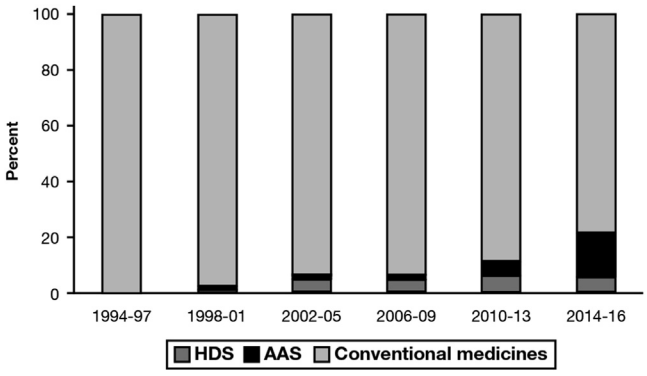

Figure 1. Secular trends in drug-induced liver injury cases enrolled in the Spanish DILI registry from 1994 to 2016. Drug-induced liver injury induced by conventional medicines, herbal and dietary supplements (HDS), and anabolic androgenic steroids (AAS) are represented by light gray, dark gray, and black bars, respectively.

Table 1 summarizes demographic and clinical data of the HDS cases included in the present series, of which some have been previously published as case reports.[25] Twelve (37%) cases were induced by single ingredient products and 20 (63%) were induced by multi-ingredient products. The most frequent indication for the intake of HDS products was weight loss, in 15 cases (47%). In the rest of the patients, the natural supplements were used to relieve symptoms of menopause, anxiety, pain, fatigue, constipation, dyspepsia, peripheral vein insufficiency, and diabetes mellitus.

A comparative analysis between DILI cases induced by HDS, AAS, and conventional drugs is shown in Table 2. Cases attributed to HDS were younger compared with cases induced by conventional drugs, with a mean age of 48 years vs 55 ($P < .001$), and a higher proportion of HILI patients were women (63%) compared with DILI cases induced by other drugs (49%; $P < .001$). Median of treatment duration in the HDS cases was 47 days and the median latency period between initial consumption and the start of symptoms was 29 days. These parameters did not differ significantly between any of the groups. The most frequent symptom for which the HILI patients sought medical consultation was jaundice (78%), which was present significantly less frequently than in the AAS hepatotoxicity cases (95%; $P = .02$). In the remaining HILI patients, DILI was initially detected from elevated aminotransferases. Besides, 9 of the HILI patients (28%) developed hypersensitivity features. The HILI cases presented a mean ALT value 37× ULN, and a mean AST value of 30× ULN in the first blood analysis after DILI onset. These values were significantly higher compared with the corresponding values in DILI cases due to conventional drugs (ALT19× ULN and AST18× ULN) and AAS products (ALT14× ULN and AST5.7× ULN; $P < .001$ and $P = .1$, respectively). In contrast, the HILI mean value of total bilirubin was lower compared with that of AAS cases (8.9 mg/dL vs 17 mg/dL). Similarly, the ALP mean value corresponding to HILI was lower than that corresponding to DILI induced by conventional drugs (1.5× ULN vs 2.2× ULN). Consequently, the type of liver damage most frequently found in HILI cases was hepatocellular (94%). Liver biopsy during the DILI episode was performed in 6 HILI patients and showed cholestasis with hepatitis (4 cases) and focal necrosis (2 cases).

A positive re-exposure defined by a relapse of liver injury following reintake of the substance responsible for the initial liver damage occurred in 3 of the HILI cases (9%). This re-exposure was accidental in all the cases due to absence of clinical suspicion of DILI in the first episode, or misdiagnosis of the first DILI episode. Re-exposure occurred more frequently in the HILI cases, compared with conventional medication or AAS-related DILI (9% vs 6% and 0%, respectively).

Table 1. Demographic and Clinical Characteristics of DILI Cases Due to Herbal and Dietary Supplements Included in the Spanish DILI Registry

Brand Name (Botanical)	Age (y)/ SexS	Rechallenge	HC (n)	Chol (n)	Jaundice (n)	Positive autoantibodies (n)	Hospitalization (n)	Outcome (year)	CIOMS-RUCAM (n)
Varicid (*Aesculus hippocastanum*, Horse Chestnut)	69/F	No	1	-	1	-	1	Unknown (2005)	Probable
Green tea (*Camellia sinensis*)[a]	48/M	No	1	-	1	-	1	Unknown (2007)	Probable
Green tea (*Camellia sinensis*)[a]	26/F	Yes	1	-	1	1	1	Unknown (2003)	Probable
Exolise (*ethanolic extract of Camellia sinensis*)	27/F	No	1	-	1	-	-	Resolved (2002)	Probable
Xenodrine (*Camellia sinensis*)	33/M	No	1	-	1	-	1	Unknown (2010)	Probable
Thermofast (*Camellia sinensis*)	18/F	No	1	-	1	-	1	Resolved (2011)	Probable
Lipo-Burn (*Camellia sinensis*)	50/F	No	1	-	1	-	1	Resolved (2010)	Possible
Green tea (*Camellia sinensis*)[a]	47/M	No	1	-	1	-	1	Unknown (2009)	Probable
Camilina (*Camellia sinensis*)	23/F	Yes	1	-	1	-	1	ALF with spontaneous resolution (1997)	Highly Probable
SHIP (*Cassia angustifolia*, Senna)	78/M	No	1	-	1	-	1	Unknown (2000)	Probable
Iberogast (*Chelidonium majus*, Greater Celandine)	37/M	No	1	-	1	-	1	Liver Tx (2012)	Probable
CH-14 Copalchi (*Coutarea latiflora*)	64/M	No	1	-	-	-	-	Resolved (2006)	Probable
Chitosan[b]	42/F	No	1	-	-	-	1	Unknown (2005)	Possible
K7 (*Equisetum arvense*, Field Horsetail)	60/F	No	1	-	-	-	1	Resolved (2011)	Probable
Ginkgo Max (*Ginkgo biloba*)	76/F	No	1	-	1	-	1	Unknown (2014)	Probable
Vaira Vati (*Glycyrrhiza glabra*, Licorice)	46/M	No	-	1	1	-	-	Unknown (2008)	Possible
Herbalife products	57/F	No	1	-	1	-	-	Unknown (2007)	Probable
Herbalife products	46/M	No	1	-	1	-	-	Resolved (2010)	Probable
Herbalife products	50/F	No	1	-	1	1	1	Resolved (2006)	Probable
Herbalife products	49/F	Yes	1	-	1	1	1	Resolved (2008)	Highly probable
Herbalife products	53/F	No	1	-	1	-	1	Resolved (2005)	Probable
Herbalife products	49/M	No	1	-	1	-	1	Unknown (2007)	Possible
Isoflavones[a]	50/F	No	1	-	1	-	-	Resolved (2012)	Possible
Phyto soya[c]	52/F	No	1	-.	-	-	-	Resolved (2003)	Possible
Phyto soya[c]	57/F	No	1	-	-	-	-	Resolved (2005)	Possible
Rhamnus purshiana (Cascara Sagrada)[a]	44/F	No	1	-	1	-	-	Unknown (2003)	Probable
Lipograsil (*Rhamnus purshiana*, Cascara Sagrada)	36/F	No	1	-	1	1	-	Unknown (2003)	Possible
Permixon (*Serenoa repens*, Saw Palmetto)	44/M	No	1	-	-	-	-	Resolved (2015)	Possible
Capslim (*Thevetia peruviana*, Yellow Oleander)	66/M	No	1	-	1	1	1	Unknown (2012)	Probable
TrimFast	38/F	No	1	-	1	-	-	Death (2015)	Possible
Valeriana officinalis (Valerian)[a]	55/M	No	-	1	1	1	1	Resolved (2001)	Probable
Sonnok (*Valeriana officinalis*, Valerian)	50/F	No	1	-	-	1	-	Resolved (2005)	Possible

Chol, cholestatic damage; CIOMS/RUCAM, Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method; HC, hepatocellular damage; M, male; Tx, transplant.

[a]Brand name not reported.

[b]The main components of chitosan are polysaccharide from exoskeleton of crustaceans.

[c]Phyto soya contains Glycine max.

Table 2. Comparison of Demographics, Clinical and Laboratory Parameters Between 856 Spanish Hepatotoxicity Cases Induced by HDS, Conventional Medications, and AAS

	HDS (n = 32)	Conventional Medicines (n = 804)	AAS (n = 20)	*P* Value
Age, *y*	48 (18–78)[a,b]	55 (11–90)	31 (20–49)[c]	<.001
Female	20 (63)[b]	396 (49)	0[c]	<.001
BMI, g/m^2	26 (20–40)	26 (15–42)	24 (19–32)	.2
Clinical presentation				
Jaundice	25 (78)	534 (67)	19 (95)[c]	.02
Hospital admission	19 (63)	412 (58)	16 (84)[c]	.06
Hypersensitivity features	9 (28)	304 (51)	8 (40)	.5
Eosinophilia	3 (9)	183 (24)	2 (10)	.06
Lymphopenia	5 (17)	161 (24)	3 (16)	.5
Positive autoantibody titres	7 (27)	148 (23)	1 (5.0)	.2
Duration of treatment, *d*	71/47 (1–540)	85/25 (1–2313)	60/47 (16–274)	.8
Time to DILI onset, *d*	55/29 (0–365)	77/23 (0–2313)	63/47 (7–300)	.8
Type of liver injury				.005
Hepatocellular	30 (94)[a,b]	493 (63)	12 (60)	
Cholestatic/mixed	2 (6.2)	291 (37)	8 (40)	
Laboratory parameters at onset				
TBL, mg/dl	8.9 (0.4–24)[b]	7.1 (0.2–46)	17 (1.8–33)[c]	<.001
AST, ×*ULN*	30 (1.3–76)[b]	18 (0.2–197)	5.7 (0.6–53)	.1
ALT, ×*ULN*	37 (0.6–84)[a,b]	19 (0.5–203)	14 (1–142)	<.001
GGT, ×*ULN*	4.9 (0.3–18)[a]	8.1 (0.2–79)	1.8 (0.6–5.9)[c]	.002
ALP, ×*ULN*	1.5 (0.4–8.5)	2.2 (0.2–22)	1.3 (0.1–2.3)	.05
Outcome				
Liver transplant	1 (3.1)	14 (1.7)	0	.7
Death	1 (3.1)	19 (2.4)	0	.8
Time to resolution, *d*	84 (48–427)	131 (5–3020)	72 (76–218)	.6
Rechallenge	3 (9)	47 (5.8)	0	.4
Severity				.048
Mild	7 (22)	247 (32)	1 (5.0)	
Moderate+severe	23 (72)	500 (62)	19 (95)	
Fatal/liver transplantation	2 (6.2)	33 (4.1)	0	
Associated diseases				
Diabetes	2 (6.2)	100 (12)	0	.1
Hypertension	4 (17)	163 (28)	0[c]	.01

Values are mean (range), n (%), or mean/median (range). Severity index: mild: elevated alanine transaminase (ALT)/alkaline phosphatase (ALP) meeting drug-induced liver injury (DILI) criteria with total bilirubin <2 mg/dL; moderate: elevated ALT/ALP with total bilirubin ≥ 2 g/dL; severe: elevated ALT/ALP and 1 of the following: ascites, encephalopathy, international normalized ratio >1.5, or other organ failure considered to be due to DILI; fatal: death or transplantation due to DILI. Hypersensitivity features: present 1 or more positive features as fever, rash, arthralgia, peripheral eosinophilia, or lymphopenia.

AAS, anabolic androgenic steroids; AST, aspartate aminotransferase; BMI, body mass index; HDS, herbal and dietary supplements; TBL, serum total bilirubin; ULN, upper limit of normal.

[a] $P < .05$ HDS vs conventional medicines.

[b] $P < .05$ HDS vs AAS.

[c] $P < .05$ AAS vs conventional medicines.

In relation to severity, 19 HILI cases needed hospitalization (63%). Three patients developed ALF, 1 of whom recovered without liver transplant, 1 underwent a liver transplantation, and 1 died before a liver transplantation was possible. HILI showed higher severity than the other groups with an elevated number of fatal/liver transplant cases (6% vs 4% vs 0%; $P = .048$). Complete resolution of the clinical picture was evident in 16 HILI patients. All of these cases resolved before 1 year and consequently did not develop chronic DILI. Lesser comorbidity, including diabetes and hypertension, was observed in cases due to HDS as compared with those attributed to conventional medicines.

Application of the CIOMS/RUCAM scale produced a probability score of highly probable in 2 patients (6%), probable in 19 patients (59%), and possible in 11 patients (36%).

Discussion

Herbal and dietary supplement-induced liver injury is an increasing healthcare problem. In contrast to medicinal products including Traditional Herbal Medicinal Products which are regulated in the European Union with regard to efficacy, safety and quality standards,[1,2] the lack of regulation of "natural" dietary supplemental products, together with the limited awareness of physicians and consumers about possible harmful effects of these supplements, reflect the need for research and reporting in this field.[26] In a previous report from the Spanish DILI registry published in 2008, we described 13 HILI cases, which reflected a prevalence of 2% of all DILI cases.[11] The current study demonstrates that the overall trend in HILI in the Spanish DILI registry has not

changed significantly over time, with the proportion of HILI cases ranging between 2% and 6% over the time period 1998–2016. An important contributing factor might be the available Directive 2002/46/EC, which harmonizes within Europe the monitoring processes of food supplements.[27] In the United States herbs are defined as dietary supplements and undergo less strict regulation compared with conventional drugs.[3] In contrast, in Europe herbs may be included either as a dietary supplement or a medicinal product.

The current 32 HILI cases correspond to almost 4% of the DILI cases included to date in the Spanish DILI registry. This is similar to a recent study in Berlin, which reported a HILI frequency of 5.1%, but is lower than the 16% reported proportion of HDS cases in Iceland and the United States, which both combined HILI and AAS hepatotoxicity.[9,16,28] This is, however, not the only reason for the lower frequency in our registry as combining our 32 HILI and 20 AAS-induced liver injury cases will only increase the total frequency to 6% of the cases in the Spanish DILI registry. Other reasons for the lower prevalence of HILI in Spain may be a lower consumption of HDS products in the country, misdiagnoses, or under-reporting of HDS cases.

The majority of the HDS cases in the current series were induced by multi-ingredient products; however, we have attempted to identify the most probable single causative ingredient based on known hepatotoxicity potentials of the ingredients. The most frequent single herbal ingredient involved in HDS hepatotoxicity was *Camellia sinensis* (green tea) in 25% of cases. Of the 63% of cases related to multi-ingredient products, Herbalife products predominated, which is in line with the results reported by Björnsson et al.[9] Noticeably, Herbalife case identifications spanned from 2006 to 2012, with no further cases in later years, which might have been be related to changes in the composition of the product. The fact that the majority of the HDS cases were induced by multi-ingredient HDS products in the current study may stem from the ever-growing number of new available multi-ingredient HDS products, particularly for internet purchases.

Similar to the DILIN study from the United States,[7] the main prescription reason for HDS use in the current cohort was weight loss, in almost half of the reported cases. Rates of obesity have increased over the last decades, with a reported prevalence in the United States of 35% in men and 40.4% in women.[29] Increased public awareness regarding obesity-related health problems, along with the social pressure concerning body image, has given way to complementary and alternative medicine, including HDS, as weight loss shortcuts.[30] In a survey conducted among 3500 adults in the United States, 34% of adults that were seriously attempting to lose weight reported using dietary supplements.[31]

Unlike DILI patients caused by conventional drugs or AAS, more HILI patients were women (63%). This may be due to women being more prone to use supplements as well as being more concerned about weight loss.[5] The HILI and AAS patients were both younger than patients with conventional drug-related liver injury. This is probably related to consumption habits, and increased rate of comorbidities that need treatment with conventional drugs as the patient grows older. These results were similar to those reported in recent studies.[7,19]

The pattern of liver injury was hepatocellular in 94% of the HILI patients. This proportion was significantly higher than what was seen among DILI cases induced by conventional drugs (63%) and AAS products (60%). Consequently, the HILI patients presented higher ALT values, but less frequently hypersensitivity features. Hepatocellular type of liver damage, higher aminotransferase levels, and normal or low peripheral eosinophil counts have all been associated with higher risk of a severe outcome and could be the reason for the higher risk of ALF in this group of patients.[32,33] It is unclear whether a common pathogenic mechanism of toxicity could be present, given that different compounds are implicated in HDS hepatotoxicity. However, in a study by the Acute Liver Failure Study Group, the CAM population showed higher transplantation rates, but no differences related to type of liver injury or sex when compared with cases induced by prescription medicines.[19]

Despite that overall serious outcomes were not significantly different between the 3 groups in the current study, 3 of the HILI patients progressed to ALF (9.4%), requiring serious medical interventions. These results are not in concordance with the results of the DILI group or with our previous report in 2008, where patients with HILI were more frequently hospitalized and associated with a higher risk of a severe outcome compared with DILI due to prescription drugs.[7,11] While the frequency of fatal/transplant cases (6.2%) was higher among the HILI cases compared with the DILI cases induced by conventional medications in the current study, the difference did not reach statistical significance probably due to the limited number of HILI cases included in the study. Similar to conventional medications, HILI that caused hepatocellular damage and resulted in jaundice had a fatality rate of 8.7%, which is in line with Hy's law.

An interesting fact is that rechallenge was more prevalent in the HILI group. The main reason of readministration of the culprit HDS product was a misdiagnosis and/or unawareness of the first episode. Hence, rechallenge can be avoided with a correct causality assessment and detailed information given to the patient regarding the cause of the liver injury.[34] However, the diagnosis of HILI has additional difficulties compared with the diagnosis of conventional drug-related DILI.[35,36] HDS products are generally promoted as being "natural," and therefore perceived as innocuous by consumers and many health care professionals. Thus, patients tend to underreport HDS use to their physicians. According to Verma et al[37], 31%–40% of patients do not disclose HDS

use. Finally, the CIOMS/RUCAM scale was applied to all HILI cases in the current study as there is not yet a specific method for HDS-related DILI assessment, which remains an unmet need. The CIOMS/RUCAM usually underscores the causality assessment in this setting, particularly when considering multi-ingredient products whose concentrations and biologic activity may vary. This makes the identification of a single causative agent very difficult.[10] The main limitations when applying the CIOMS/RUCAM scale are the lack of previous information about adverse events induced by these products or incomplete time criteria.[38] In DILI cases involving a drug and a concomitant herbs containing dietary supplements, the drug usually receives a higher CIOMS score due to hepatotoxic potential included in the summary of product characteristics, while this information is not available for herbal products. Nevertheless, 2 of the HDS cases in the current series had a CIOMS score above 8 (highly probable). This was however due to rechallenge, which rarely occurs in DILI.

Despite the fact that the HILI cases included in this study may not be representative of all forms of HILI, but is merely the tip of the iceberg, the present study is a comprehensive analysis of all HILI cases reported to the Spanish DILI registry to date. This study provides relevant information about clinical features associated with HILI, and highlights the importance of identifying all medicinal products, prescription drugs as well as HDS products, taken by patients who develop liver abnormalities. An initial suspicion of DILI, correct diagnosis and reporting of DILI cases will lead not only correct treatment options and improved outcomes, but also to reduce the risk of rechallenge and its consequences.

References

1. Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use. Offic J Eur Union 2001; L311:67.
2. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Offic J Eur Union 2004;L136:85–90.
3. 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, 2017.
4. Garcia-Alvarez A, Egan B, de Klein S, et al. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One 2014;9:e92265.
5. Bailey RL, Gahche JJ, Miller PE, et al. Why US adults use dietary supplements. JAMA Intern Med 2013;173:355–361.
6. Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis 2014;34:172–193.
7. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014;60:1399–1408.
8. Seeff LB, Bonkovsky HL, Navarro VJ, et al. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology 2015;148:517–532.
9. Björnsson ES, Bergmann OM, Björnsson HK, et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013;144:1419–1425.
10. Andrade RJ, Medina-Caliz I, Gonzalez-Jimenez A, et al. Hepatic damage by natural remedies. Semin Liver Dis 2018;38:21–40.
11. 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; 100:688–695.
12. Zhou Y, Yang L, Liao Z, et al. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21,789 patients. Eur J Gastroenterol Hepatol 2013; 25:825–829.
13. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol 2012; 107:1380–1387.
14. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005; 129:512–521.
15. Devarbhavi H, Dierkhising R, Kremers WK, et al. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010;105:2396–2404.
16. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148:1340–1352.
17. Bessone F, Hernandez N, Lucena MI, et al. The Latin American DILI registry experience: a successful ongoing collaborative strategic initiative. Int J Mol Sci 2016;17:313.
18. Dağ MS, Aydınlı M, Oztürk ZA, et al. Drug- and herb-induced liver injury: a case series from a single center. Turk J Gastroenterol 2014;25:41–45.
19. Hillman L, Gottfried M, Whitsett M, et al. Clinical features and outcomes of complementary and alternative medicine Induced acute liver failure injury. Am J Gastroenterol 2016;111:958–965.
20. Goldberg DS, Forde KA, Carbonari DM, et al. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. Gastroenterology 2015;148:1353–1361.
21. Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. Aliment Pharmacol Ther 2015; 41:116–125.
22. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990;11:272–276.
23. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806–815.
24. Danan G, Benichou C. Causality assessment of adverse reactions to drugs I. A novel method based on the conclusions of international consensus meeting: application to drug-induced liver injures. J Clin Epidemiol 1993;43:1323–1330.
25. Bruguera M, Herrera S, Lázaro E, et al. Hepatitis aguda asociada al consumo de Copalchi. A propósito de 5 casos. Gastroenterol Hepatol 2007;30:66–68.

26. Navarro VJ, Khan I, Björnsson E, et al. Liver injury from herbal and dietary supplements. Hepatology 2017;65:363–373.
27. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Offic J Eur Union 2002;L183:51–57.
28. Douros A, Bronder E, Andersohn F, et al. Herb-induced liver injury in the Berlin case-control surveillance study. Int J Mol Sci 2016;17:E114.
29. Flegal KM, Kruszon-Moran D, Carroll MD, et al. Trends in obesity among adults in the United States, 2005 to 2014. JAMA 2016;315:2284–2291.
30. Esteghamati A, Mazaheri T, Vahidi Rad M, et al. Complementary and alternative medicine for the treatment of obesity: a critical review. Int J Endocrinol Metab 2015;13:e19678.
31. Pillitteri JL, Shiffmann S, Rohay JM, et al. Use of dietary supplements for weight loss in the United States: results of a national survey. Obesity 2008;16:790–796.
32. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014; 147:109–118.
33. Pachkoria K, Lucena MI, Crespo E, et al. Analysis of IL-10, IL-4 and TNF-alpha polymorphisms in drug-induced liver injury (DILI) and its outcome. J Hepatol 2008;49:107–114.
34. 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;100:278–284.
35. García-Cortés M, Robles-Díaz M, Ortega-Alonso A, et al. Hepatotoxicity by dietary supplements: a tabular listing and clinical characteristics. Int J Mol Sci 2016;17:537.
36. Teschke R, Andrade RJ. Drug, Herb, and Dietary Supplement Hepatotoxicity. Int J Mol Sci 2016;17:1488.
37. Verma S, Thuluvath PJ. Complementary and alternative medicine in hepatology: review of the evidence of efficacy. Clin Gastroenterol Hepatol 2007;5:408–416.
38. García-Cortés M, Stephens C, Lucena MI, et al. Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol 2011;55:683–691.

Reprint requests
Address requests for reprints to: M. Isabel Lucena, Departamento de Farmacología, Facultad de Medicina, Boulevard Louis Pasteur, 32 Campus de Teatinos s/n, 29071 Málaga, Spain. e-mail: lucena@uma.es and Miren Garcia-Cortes, UGC Ap Digestivo. Hospital Universitario Virgen de la Victoria, Departamento de Medicina, Facultad de Medicina, Universidad de Málaga, Boulevard Louis Pasteur, 32 Campus de Teatinos s/n 29071, Málaga, Spain. e-mail: mirengar1@hotmail.com; fax: (+34) 952 131572.

Acknowledgments
The funding sources had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report or in the decision to submit the manuscript for publication.

The authors are grateful to D. Ramon Hidalgo of the Servicio Central de Informática de la Universidad de Malaga for his invaluable help in the statistical analysis. Pere Ginès is a recipient of a research prize from the ICREA ACADEMIA, Barcelona.

Participating clinical centers in the Spanish DILI Registry: Hospital Universitario Virgen de la Victoria, Málaga (coordinating center): RJ Andrade, MI Lucena, C Stephens, M García-Cortés, M Robles-Díaz, I Medina-Cáliz, J Sanabria, B García-Muñoz, R Alcántara, I Moreno, A Gonzalez-Jimenez, A Ortega-Alonso, R Sanjuán-Jiménez, M Quirós, F Martín-Reyes, A Papineau; Hospital Regional Universitario de Málaga: M Jiménez-Pérez, R González-Grande.

Hospital Torrecárdenas, Almería: MC Fernández, G Peláez, M Casado, M González-Sánchez; Hospitales Universitarios Virgen del Rocío y de la Macarena, Sevilla: M Romero-Gómez, R Calle-Sanz, R Millán-Domínguez, B Fombuena, R Gallego, L Rojas, A Rojas, J Ampuero, JA del Campo, A Gil Gómez, E Vilar; Hospital de Mendaro, Guipúzcoa: A Castiella, EM Zapata, L Zubiaurre; Hospital Costa del Sol, Marbella, Málaga: JM Navarro, IM Méndez-Sánchez, A Chaves; Hospital Sant Pau, Barcelona: G Soriano, C Guarner, EM Román; Hospital Morales Meseguer, Murcia: H Hallal, E García-Oltra, JC Titos-Arcos, A Pérez-Martínez, C Sánchez-Cobarro, JM Egea-Caparrós; Hospital de Donostia, San Sebastián: J Arenas, MI Gomez-Osua, A Gómez-García, FJ Esandi; Hospital de Basurto, Bilbao: S Blanco, P Martínez-Odriozola; Hospital Alto Deba Mondragón, Guipúzcoa: P Otazua; Hospital Universitario San Cecilio, Granada: J Salmerón, A Gila, R Quiles; Hospital Clínico Valladolid: JM González, S Lorenzo; Hospital La Fe, Valencia: M Prieto, I Conde, Amiel, M Berenguer, M García-Eliz; Hospital de Sagunto, Valencia: J Primo, JR Molés, A Garayoa; Hospital de Laredo, Cantabria: M Carrascosa; Hospital 12 de Octubre, Madrid: E Gómez- Domínguez; Hospital Germans Trias i Pujol, Badalona, Barcelona: E Montané, AL Arellano, AM Barriocanal, Y Sanz, RM Morillas, M Sala, H Masnou, M Farré; Hospital Clínic, Barcelona: M Bruguera, P Gines, S Lens, JC García.

Hospital Universitario de Canarias, La Laguna, Tenerife: A Aldea-Perona, M Hernández-Guerra, M Moreno-San Fiel, C Boada-Fernández del Campo; Hospital Infanta Elena, Valdemoro, Madrid: M Tejedor, R González-Ferrer; Hospital de Alcorcón, Alcorcón, Madrid: C Fernández, M Fernández-Gil; Hospital Reina Sofía, Córdoba: JL Montero, M de la Mata; Hospital Miguel Servet, Zaragoza: J Fuentes-Olmo, EM Fernández-Bonilla; Hospital de León, León: J González-Gallego, F Jorquera; Complejo Hospitalario Universitario de Albacete, Albacete: JM Moreno, P Martínez-Rodenas, M Garrido; Hospital Puerta del Mar, Cádiz: P Rendón; Hospital Parc Taulí de Sabadell, Barcelona: M Vergara, J Sánchez Delgado; Hospital Carlos III, Madrid: J García Samaniego, A Madejón; Hospital de Galdakao: JL Cabriada; Hospital Marqués de Valdecilla, Santander: J Crespo; Hospital Virgen del Rocío: A Giráldez Gallego, M Cuaresma, R Ruíz.

Conflicts of interest
The authors disclose no conflicts.

Funding
The present study has been supported by grants of the Instituto de Salud Carlos III cofounded by Fondo Europeo de Desarrollo Regional – FEDER (contract numbers: PI12-00620, PI15-01440, AC-0073-2013, FIS PI12/00330, and FIS PI16/00043) and by the Agencia Española del Medicamento. CIBERehd is funded by Instituto de Salud Carlos III. SCReN and CIBERehd are funded by Instituto de Salud Carlos III.