Herbal and Dietary Supplements-Induced Liver Injury in Latin America: Experience From the Latindili Network

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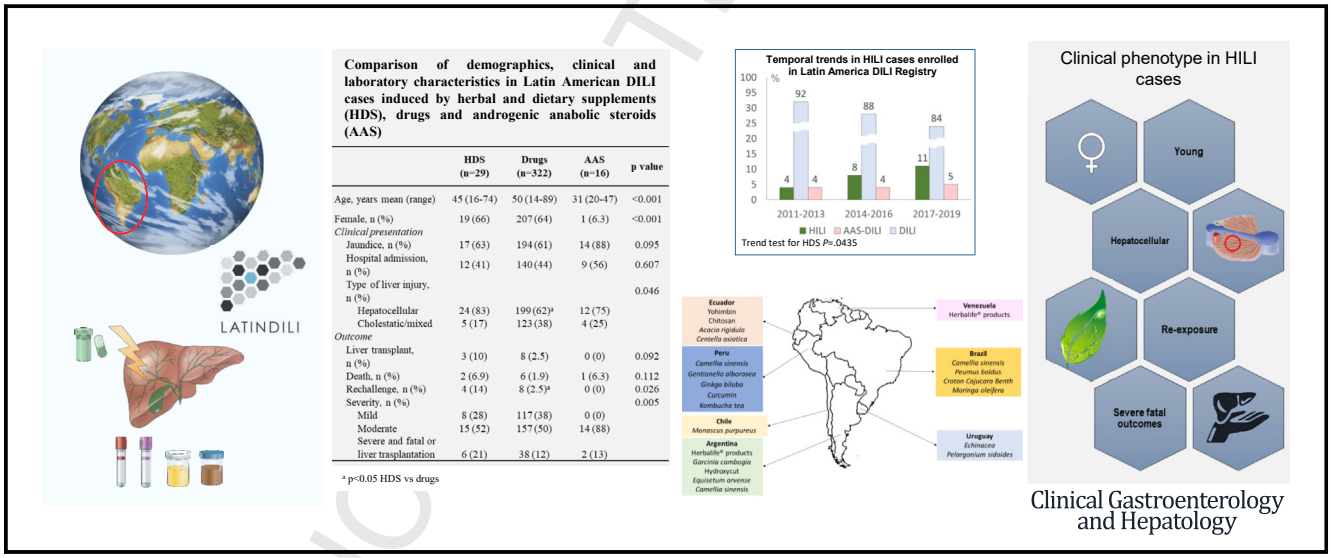

BACKGROUND: **Herbal and dietary supplements (HDS) consumption, a growing cause of hepatotoxicity, is a common practice among Latin-American populations. Objectives: To evaluate clinical, laboratory features and outcome in HDS-hepatotoxicity included in the Latin America-Drug Induced Liver Injury (LATINDILI) Network.**

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Abbreviations used in this paper: AAS, anabolic androgenic steroids; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; DILI, drug-induced liver injury; DILIN, Drug-Induced Liver Injury Network; HDS, herbal and dietary supplements; HILI, herbal-induced liver injury; LATINDILIN, Latin America DILI Network; RUCAM, Roussel Uclaf Causality Assessment Method.

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METHODS: **A total of 29 adjudicated cases of HDS hepatotoxicity reported to the LATINDILI Network from October 2011 through December 2019 were compared with 322 DILI cases due to conventional drugs and 16 due to anabolic steroids as well as with other series of HDS-hepatotoxicity.**

RESULTS: **From 367 DILI cases, 8% were attributed to HDS. An increasing trend in HDS-hepatotoxicity was noted over time ($p = .04$). *Camellia sinensis*, Herbalife® products, and *Garcinia cambogia*, mostly used for weight loss, were the most frequently adjudicated causative agents. Mean age was 45 years (66% female). Median time to onset was 31 days. Patients presented typically with hepatocellular injury (83%) and jaundice (66%). Five cases (17%) developed acute liver failure. Compared to conventional medications and anabolic steroids, HDS hepatotoxicity cases had the highest levels of aspartate and alanine transaminase ($p = .008$ and $p = .021$, respectively), had more re-exposure events to the culprit HDS (14% vs 3% vs 0%; $p = .026$), and had more severe and fatal/liver transplantation outcomes (21% vs 12% vs 13%; $p = .005$). Compared to other DILI cohorts, less HDS hepatotoxicity cases in Latin America were hospitalized (41%).**

CONCLUSIONS: **HDS-hepatotoxicity in Latin-America affects mainly young women, manifests mostly with hepatocellular injury and is associated with higher frequency of accidental re-exposure. HDS hepatotoxicity is more serious with a higher chance of death/liver-transplantation than DILI related to conventional drugs.**

Keywords: Herbal-Induced Liver Injury; Herbal and Dietary Supplements; Drug-Induced Liver Injury; Liver Toxicity; Hepatotoxicity; LATINDILI Network; Latin America.

Botanical products are used as dietary supplements or herbal medicines worldwide. It is increasingly recognized that some herbal and dietary supplements (HDS) may also cause adverse effects, including liver toxicity in analogy to conventional drugs. Indeed, HDS may induce any type of liver injury ranging from mild increase in liver parameters to acute liver failure (ALF).[1,2]

In most countries herbal products are considered as dietary supplements and therefore lack the oversight and strict regulatory requirements applied to prescription drugs to demonstrate quality, efficacy, and safety.[3] Epidemiology of herbal products use and liver toxicity demonstrates wide variations between different countries. The United States Drug-Induced Liver Injury Network (DILIN) has estimated that HDS products account for 16% of drug-induced liver injury (DILI) cases (10% when excluding bodybuilding supplements), with an increase from 7% in 2004–2005 to 20% in 2013–2014.[4] These figures are similar to the ones reported in a prospective study carried out in Iceland.[5] A more recent 1-year prospective population-based study carried out in the United States yielded a DILI incidence rate of 2.7 cases per 100,000 adults, where 43% were HDS related.[6] However, a lower prevalence was found in Spain (4%)[7] and similarly (5%) in a case-control surveillance study conducted in Germany.[8]

Alternative medicine and HDS are more popular in Africa, Latin America, and Asia, where different types of traditional practice, such as unani, ayurveda, kampo, or traditional Chinese medicine, have been used for centuries and are even integrated into the health care system.[9] Nevertheless, the prevalence of HDS-induced liver injury (HILI) in these countries is highly variable, ranging from 12% in Turkey or 28% in China to more than 70% in South Korea and Singapore. Curiously, in India with an extended use of ayurvedic medicine, prevalence of HILI remains lower than in Western countries (1.3%).[10–14]

Regulation of HDS is also heterogeneous and differs between countries. Even among 21 Latin American countries with an important traditional market for HDS, there are considerable differences in policies and regulations on traditional medicines.[9] The main consequence of this heterogeneity is a less regulated market. The World Health Organization Traditional Medicine Strategy for the upcoming years is expected to help strengthen regulatory frameworks and safety monitoring in Latin America.[15]

The use of HDS in Latin America is widely accepted; however, there are limited data on profile and pattern of use. Understandably, characterization of the phenotype of HILI was one of the priorities of the Latin America DILI Network (LATINDILIN), set up in 2011 with the support of the Spanish DILI Registry and the Latin American Association for the Study of the Liver,[16,17] which aimed at covering this gap by prospective and standardized collection of well-vetted cases of DILI and HILI. In a recent systematic review, Santos et al[18] found only 17 reports including 23 cases of HILI published in Latin America from 1976 to 2020. This study confirms the low reporting of hepatotoxicity associated with "natural products" and the selection bias in publication of hepatic reactions because these series were enriched in cases with a worst outcome and chronicity.[18]

The aim of the present study was to evaluate the distinct clinical characteristics and outcome of liver injury adjudicated to HDS in the LATINDILIN and compare this information with results from other series of HDS-related liver injury.

What You Need to Know

Background

Herbals and dietary supplements (HDS) represent an important traditional medicine market in Latin America. Whereas regulatory requirements of HDS differ across countries, their potential for causing hepatotoxicity is a growing concern.

Findings

Hepatotoxicity due to HDS in Latin America occurs mainly in young women with hepatocellular type of injury. Liver injury induced by HDS was found to be more serious than that of conventional medication with a higher proportion of death and liver transplantation, as well as accidental re-exposure to the causative agent.

Implications for patient care

Physicians and health authorities should increase awareness of the risk of hepatotoxicity associated with unregulated HDS consumption. This analysis may help clinicians in the prevention, identification, and management of HDS hepatotoxicity in Latin America.

Materials and Methods

Cases of HDS-induced liver injury reported to the LATINDILIN from October 2011 through December 2019 were included in this study. The LATINDILIN is a prospective network of countries collecting DILI cases with demographics, clinical and laboratory parameters, imaging, and histologic (when available) information both at DILI recognition and during follow-up.[16] The study protocols were approved by local ethics committees. All subjects gave informed written consent.

After informed consent is given and a standardized report form is completed by the clinician in charge, a case description is first sent to the coordinating physician in each country before it is reported to the coordinating center located at the University of Malaga (Spain) where it is reevaluated by a panel of 3 DILI experts before inclusion in the database.[17] The operational structure of the network, data recording, and case ascertainment have been previously described.[17] The structured report form is used to record pharmacologic and clinical patient data. This form also includes information on the temporal relationship between initial intake of HDS and onset of liver disease, outcome of liver damage and blood test results, and imaging tests to rule out other causes of liver disease. Causality assessment was made using the Roussel Uclaf Causality Assessment Method (RUCAM) scale.

The biochemical DILI criteria used were those defined by an international DILI expert group.[19] The pattern of liver injury was determined by using alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activity expressed as a multiple of the upper limit of normal to calculate the ratio of ALT/ALP from the first available blood test after DILI recognition.[19] HDS hepatotoxicity cases were classified as mild, moderate, severe, or fatal/liver transplantation on the basis of the DILI severity classification[19] and were also assessed as to whether they fulfilled nR-based Hy's law criteria.[20]

Natural products were classified as single or multi-ingredient herbal products and dietary supplements. Bodybuilding dietary supplements containing anabolic androgenic steroids (AAS) were evaluated separately and included in the analysis for comparative purposes.

Descriptive analyses were performed. Differences in categorical variables were tested with the exact χ^2 test. Differences in continuous data were assessed with the Student *t* test/analysis of variance or the Mann-Whitney *U* test/Kruskal-Wallis test as appropriate. Post hoc analysis with Bonferroni correction for multiple comparisons was performed. The Cochran-Armitage test for linear trend was used to calculate temporal trends in hepatotoxicity cases. In all analyses, P value $<.05$ was considered as statistically significant. All analyses were performed by using SPSS version 19.0 (IBM Corp, Armonk, NY).

Results

Characteristics of Herbal and Dietary Supplements–Related Liver Injury Cases Reported to the Latin America Drug-Induced Liver Injury Network

From a total of 367 DILI cases included in the LATINDILIN from October 2011 through December 2019, 29 cases (8%) adjudicated to HDS were detected. HDS was the third most common culprit agent class, behind anti-infectives (32%) and musculoskeletal drugs (14%) and similar to cardiovascular and nervous system drugs (8% for both). Only HDS hepatotoxicity cases showed a significant increase over the years from 4% in the period 2011–2013 to 11% in 2017–2019 ($P = .0435$) (Figure 1).

A detailed description of each HDS DILI case is shown in Supplementary Tables 1 and 2. The most frequently reported causative agents were *Camellia sinensis* (green tea), Herbalife products, and *Garcinia cambogia*. Eleven cases (38%) were induced by single ingredient products, whereas the remaining 18 cases (62%) were due to multi-ingredient compounds. The most frequent therapeutic indication was weight loss in 17 cases (59%). Argentina was the country contributing the most cases (9), followed by Brazil (7 cases), and Peru (5 cases).

Patient mean age was 45 years, and 66% were female. The median time to onset was 31 days. The most common reason for consultation was jaundice in 19 patients (68%), and hepatocellular was the most common

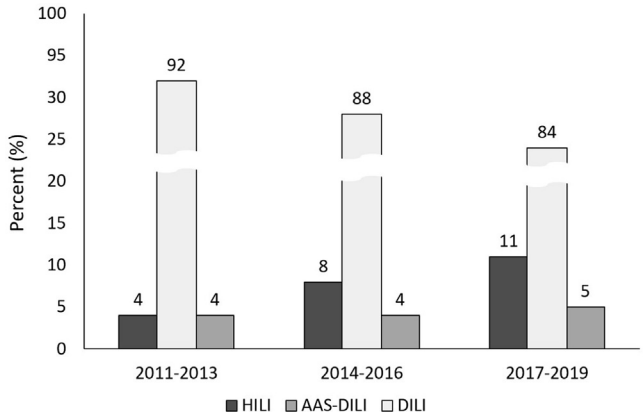


Figure 1. Trends in herbal and dietary supplements–induced liver injury cases included in LATINDILI Network from 2011 through 2019. *P* for trend for HILI: .0435; *P* for trend for DILI: .0696; *P* for trend AAS-DILI: .8045. AAS, anabolic and androgenic steroids; DILI, drug-induced liver injury; HILI, herbal and dietary supplements–induced liver injury.

pattern of liver injury (24 cases, 83%) (Supplementary Table 1).

In terms of severity and outcome, 12 patients required hospitalization (41%), and 5 cases (17%) that were due to *Camellia sinensis*/Herbalife products, *Garcinia cambogia*, Herbalife products, *Peumus boldus,* and *Yohimbine/Acacia rigidula* developed ALF, of whom 2 underwent liver transplantation, 2 died, and 1 resolved spontaneously. Twelve cases (41%) fulfilled nR-based Hy's law criteria. Although follow-up was lost in 6 patients before liver tests normalization, complete resolution was seen in 19 patients. RUCAM causality assessment was highly probable in 4 cases (14%), probable in 15 (52%), and possible in 10 (34%) (Supplementary Tables 1 and 2).

Herbal and Dietary Supplements–Induced Liver Injury vs Liver Injury Related to Conventional Drugs or Anabolic Androgenic Steroids

A comparison of HDS hepatotoxicity with DILI induced by conventional medications and those related to AAS included in the LATINDILIN revealed differences in mean age between the 3 groups ($P < .001$), with older HILI and DILI patients (45 and 50 years, respectively) compared with AAS patients (31 years) (Table 1). Female patients were similarly represented in HILI and DILI cases (66% vs 64%), whereas there was just 1 woman in the AAS hepatotoxicity series (6.3%). Hepatocellular damage predominated in all groups but was more frequently found in HDS-related liver injury (83% vs 62% vs 75%). Indeed, patients with hepatocellular injury that was due to HDS had the highest mean values of aminotransferases and had significantly higher values of bilirubin compared with DILI cases ($P = .043$). On the other hand, cholestatic/mixed AAS cases exhibited the highest mean values of bilirubin (Figure 2).

Four patients with HDS hepatotoxicity were accidentally re-exposed to the same causative product because of absence of clinical suspicion or misdiagnosis of the first episode. This was significantly higher than what was detected for conventional medication and AAS-DILI cases (14% vs 2.5% and 0%, respectively) ($P = .026$). Liver biopsy was performed in 31% of the HDS cases (9 cases) versus 17% of the DILI cases due to conventional medications. The HDS hepatotoxicity cases showed greater severity than the other groups, with an elevated number of severe and fatal/liver transplantation cases (21% vs 12% vs 13%; $P = .005$). Four AAS-related DILI cases (25%) developed acute renal dysfunction compared with 2 cases (6.9%) due to HDS and 22 (6.8%) related to drugs ($P = .045$).

Comparison With Other Herbal and Dietary Supplements Hepatotoxicity Series

Frequency of HDS hepatotoxicity was higher in the Latin American Registry compared with the Spanish DILI (4%). Nonetheless, when compared with other prospective DILI registries (U.S. DILIN [10%], Korean [73%], and Japanese DILI cohorts [8.7%]) and retrospective studies, especially those conducted in Asian countries (China, South Korea), prevalence of HDS hepatotoxicity remains lower in the LATINDILIN (Table 2). The Latin American HDS hepatotoxicity patients were similar with regard to age, sex, and type of liver injury to other prospective and retrospective DILI cohorts (Table 2). Hospitalization rate in Latin America and Pakistan showed the lowest rate (41% and 26%, respectively). However, in the remaining studies that reported the hospitalization rate, the frequency was higher and similar to that of the Spanish DILI Registry, ranging from 63% to 100%. In addition, the Latin America HDS hepatotoxicity series showed a proportion of ALF cases (17%) similar to the U.S. DILIN (16%) but higher compared with the Spanish DILI Registry (6%) and retrospective registries (China 7.6% and Korea 1.4%) and lower when compared with Pakistani cases (26%).

Discussion

HDS-induced liver injury is a growing concern worldwide. However, epidemiologic and clinical information of hepatotoxicity associated with these products in Latin America is very limited. The prospective LATINDILIN encompasses 7 Latin American countries, which have similarities but also differences with regard to prescription patterns, traditional medicine market, and regulatory policies.[16,17] The 29 prospectively collected liver injury cases attributed to HDS in the LATINDILIN (8%) represent the third largest cause of hepatotoxicity in this registry. The increase of HILI cases over time may be the result of several reasons, such as the current popularity of healthy lifestyles accompanied by the trend of using these

Table 1. Demographics and Clinical and Laboratory Characteristics in 367 Latin American Hepatotoxicity Cases Induced by Herbal and Dietary Supplements, Conventional Medicines, and Anabolic Androgenic Steroids

	HDS (n = 29)	Conventional medicines (n = 322)	AAS (n = 16)	*P* value
Age, *y* (mean, range)	45 (16–74)	50 (14–89)	31 (20–47)[b,c]	<.001
Female, n (%)	19 (66)	207 (64)	1 (6.3)[b,c]	<.001
BMI, *kg/m²* (median, IQR)	24 (23–28)	25 (23–28)	24 (23–26)	.838
Clinical presentation				
Jaundice, n (%)	19 (66)	194 (61)	14 (88)[c]	.074
Hospital admission, n (%)	12 (41)	140 (44)	9 (56)	.607
Duration of treatment, *days* (median, IQR)	41 (23–93)	31 (11–83)	59 (41–128)[c]	.018
Time to DILI onset, *days* (median, IQR)	31 (24–66)	29 (11–68)	62 (37–94)	.117
Type of liver injury, n (%)				.046
Hepatocellular	24 (83)	199 (62)[a]	12 (75)	
Cholestatic/mixed	5 (17)	123 (38)	4 (25)	
Liver biopsy, n (%)	9 (31)	56 (17)	1 (6.3)	.097
Renal dysfunction	2 (6.9)	22 (6.8)	4 (25)[c]	.045
Hepatocellular	2 (100)	13 (59)	1 (25)	.329
Cholestatic/mixed	0 (0)	9 (41)	3 (75)	
Hepatocellular total bilirubin, *mg/dL* (mean, IQR)	0.9 (0.9–1.0)	5.0 (2.0–7.8)	8.7	.309
Cholestatic/mixed total bilirubin, *mg/dL* (mean, IQR)	NA	4.5 (2.1–4.9)	5.7 (4.2–7.5)	.195
Laboratory parameters at onset (mean, IQR)				
Total bilirubin, *mg/dL*	9.7 (1.0–17)	6.4 (1.0–8.5)	11 (5.9–15)[c]	.001
AST, × ULN	19 (5.1–25)	14 (3.0–18)	8.6 (2.0–7.8)[b,c]	.008
ALT, × ULN	22 (6.8–28)	16 (4.8–20)	13 (2.5–11)[b]	.021
GGT, × ULN	6.6 (1.6–10)	10 (3.4–12)	3.9 (1.6–6.5)[c]	.022
ALP, × ULN	1.8 (0.9–2.6)	2.4 (1.1–3.0)	1.4 (0.5–2.6)[c]	.029
Outcome				
Liver transplant, n (%)	2 (6.9)	8 (2.5)	0 (0)	.240
Death, n (%)	2 (6.9)	6 (1.9)	1 (6.3)	.112
Time to resolution, *days* (median, IQR)	54 (30–120)	67 (36–130)	90 (90–120)	.100
Rechallenge, n (%)	4 (14)	8 (2.5)[a]	0 (0)	.026
Severity, n (%)				.005
Mild	8 (28)	117 (38)	0 (0)[b,c]	
Moderate	15 (52)	157 (50)	14 (88)	
Severe and fatal/Tx	6 (21)	38 (12)	2 (13)	

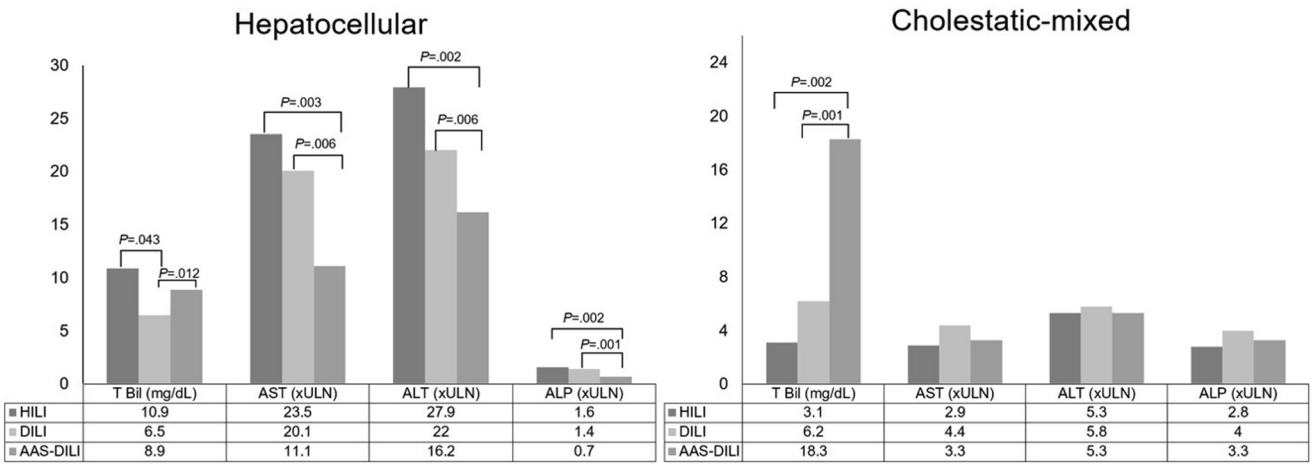
NOTE. Renal dysfunction was defined as serum creatinine values ≥1.5 mg/dL in patients with no preexisting kidney damage.
AAS, anabolic androgenic steroids; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDS, herbal and dietary supplements; IQR, interquartile range; Tx, liver transplantation.
[a]$P < .05$ HDS vs conventional medicines.
[b]$P < .05$ HDS vs AAS.
[c]$P < .05$ AAS vs conventional medicines.

products and/or increased case detection because of increasing understanding among health care providers on hepatotoxicity associated with HDS products.

The profile of HILI in our study shows similarities to what have been found in other registries. It was more frequent in young women, where these products were mainly used for weight loss, in concordance with previously reported information from the Spanish DILI Registry and U.S. DILIN cohorts.[4,7] In addition, hepatocellular type of injury predominated in our series in line with other studies, underscoring that this phenotype is characteristic of HILI and more represented than in DILI due to conventional drugs.

The diagnosis of HILI is particularly challenging.[21,22] Several factors that contribute to the complexity of causality assessment are the false safety perception of HDS by consumers and physicians, ingestion of multi-ingredient products, product adulteration, or mislabeling of HDS product.[23] In a recent report from the DILIN group, 51% of products involved in HILI had inaccurate labels.[24] Altogether, these factors may contribute to a higher proportion of re-exposure to HDS and more common indications of liver biopsy in suspected HILI cases. Thus, obtaining a detailed prescription history including HDS and over-the-counter products, along with physicians' awareness of HDS as a possible cause of liver damage, is crucial for a timely diagnosis.

However, ruling out alternative causes is sometimes a challenging issue. For example, autoantibodies were detectable in 22% of cases in the current series, which



	T Bil (mg/dL)	AST (xULN)	ALT (xULN)	ALP (xULN)
HILI	10.9	23.5	27.9	1.6
DILI	6.5	20.1	22	1.4
AAS-DILI	8.9	11.1	16.2	0.7

	T Bil (mg/dL)	AST (xULN)	ALT (xULN)	ALP (xULN)
HILI	3.1	2.9	5.3	2.8
DILI	6.2	4.4	5.8	4
AAS-DILI	18.3	3.3	5.3	3.3

Figure 2. Comparison of liver biochemical parameters among liver injury induced by herbal and dietary supplements (HDS), conventional drugs (DILI), or anabolic androgenic steroids (AAS) according to type of liver injury. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T Bil, total bilirubin; ULN, upper limit of normal.

may confound the diagnosis of HILI with idiopathic autoimmune hepatitis. Features that support the diagnosis of HDS-associated liver injury are the absence of significant fibrosis in the liver biopsy and the lack of recurrence of liver enzymes flares once steroid therapy is stopped.[25–27] In our series, 2 of the patients with positive autoantibodies underwent a liver biopsy. Case 19 (caused by Herbalife products), with high titers of antinuclear antibodies (1/320) and features of chronic hepatitis in the liver biopsy, had a positive rechallenge, confirming the toxic etiology of the liver damage. In case 18 with positive autoantibodies, the liver biopsy did not show fibrosis, although methylprednisolone was prescribed for 1 month without relapsing upon withdrawal. Another subject (case 3) with features of autoimmune hepatitis required methylprednisolone treatment for 1 year, but no further relapse of liver injury occurred after corticosteroids were stopped. The remaining cases (9 and 21) had low titers of autoantibodies and spontaneously recovered upon discontinuation of the suspected HDS. All these features make the diagnosis of hepatotoxicity more likely than that of autoimmune hepatitis. Moreover, presence of autoantibodies is commonly observed in liver toxicity induced by some HDS such as *Polygonum multiflorum*[28] or Herbalife products,[29] which supports a role of the immune system in the pathogenesis of liver injury.

Similar to the Spanish DILI registry, the most frequently attributed causative agents in HDS hepatotoxicity in the current study were *Camellia sinensis,* followed by Herbalife products. Interestingly, *Garcinia cambogia* represented the third most frequent cause in Latin America but was absent in the Spanish DILI Registry. All cases attributed to *G cambogia* were reported from Argentina, which suggest a greater use of the plant in this geographical area.

To complement the diagnostic evaluation of DILI cases, the liver-specific and widely used Council for International Organizations of Medical Sciences/RUCAM scale was applied. However, the RUCAM scale has some limitations, especially in the evaluation of HILI.[9,12] In the current series "highly probable" results were only reached in cases with positive rechallenge. The complexity of causality assessments in herbal hepatotoxicity underscores the importance of discovering new biomarkers as recently reported for *Polygonum multiflorum.*[30]

An unexpected finding in this study was the lower frequency of hospital admissions (41%) compared with those observed in Spanish and U.S. HILI series (63% and 68%, respectively).[4,7] These results could be attributed to differences in health care systems or hospital admission criteria in the Latin American countries. Outcome of HILI has been described to be worse than that of DILI associated with conventional drugs[4,31] as shown in the present study. Indeed, hepatocellular HILI cases exhibited the highest values of bilirubin and aminotransferases, variables associated with progression to ALF or death and included in prognostic models.[20,32] The nR-based Hy's law performed as expected in HILI cases that fulfilled the criteria, with 17% of liver-related death/liver transplantation. A limitation of the present study is the relatively low number of HILI cases, which precludes detecting geographical and clinical differences between the countries included in the LATINDILIN. Nevertheless, this is a prospective collection of hepatotoxicity cases Q7 related to botanical products and dietary supplements reported in Latin America, which can help health authorities and care providers to better understand and be aware of the problems associated with these products. Furthermore, our report confirms the special characteristics of HDS-induced liver injury compared with DILI, namely a higher prevalence of hepatocellular injury, female predominance, worse prognosis, higher re-exposure rate, and more challenging causality assessment.

Table 2. Studies Addressing Herbal and Dietary Supplements–Induced Liver Injury

	Latin America DILI Network	Spanish DILI Registry[7]	DILIN USA[4]	ALF USA[32]	Korea[14]	Japan[33]	Korea[34]	Beijing, China[35]	Beijing, China[12]	Shanghai, China[36]	Pakistan[37]
Type of study	Prospective	Prospective	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Total DILI cases	367	856	839	253	371	307	65	488	1985	287	462
HILI cases, n (%)	29 (8)	32 (4)	85 (10)	41 ALF (16)	270 (73)	27 (8.7)	28 (43)	488 HILI (100)	563 (28)	111 (39)	42 (9.0)
Age, *y*, mean (range)	45 (16–74)	48 (18–78)	47 (38–61)[a] (median)	41 (median)	51 (18–79) (median)	59 (30–79) (median)	ND	45 ± 13[b]	43 ± 14 [b]	ND	ND
Female, n (%)	19 (66)	20 (63)	55 (65)	16 (39)	171 (63)	ND	17 (68)	349 (72)	400 (71)	ND	ND
Jaundice	19 (66)	25 (78)	66 (78)	37 (95)	ND	ND	ND	ND	ND	ND	ND
Hospitalization	12 (41)	19 (63)	58 (68)	41 (100)[c]	270 (100)[c]	ND	28 (100)[c]	488 (100)[c]	563 (100)[c]	111 (100) [c]	11 (26.2)
Type of liver injury, n (%)											
Hepatocellular	24 (83)	30 (94)	56 (71)	32 (80)	205 (76)	22 (81)	20 (71)	420 (86)	498 (89)	41 (46)	ND
Cholestatic/ mixed	5 (17)	2 (6)	10 (13)/13 (17)	1 (2)/7 (18)	24 (9)/30 (11)	2 (7)/3 (11)	6 (21)/2 (7)	31 (6)/37 (8)	27 (5)/38 (7)	29 (29)/41 (42)	ND
Liver transplant, n (%)	2 (7)	1 (3)	11 (13)	23 (56)	2 (0.7)	0	0	1 (0.2)	2 (0.4)	0	ND
Death liver-related, n (%)	2 (7)	1 (3)	3 (4)	9 (22)	2 (0.7)	0	0	19 (3.9)	26 (4.6)	0	10 (24)
Rechallenge, n (%)	4 (14)	3 (9)	ND	ND	ND	ND	ND	35 (7.2)	50 (8.9)	ND	ND
Causality assessment	RUCAM	RUCAM	DILIN Expert Opinion	DILIN Expert Opinion	RUCAM	DDW-J 2004 score and RUCAM	RUCAM	RUCAM	RUCAM	RUCAM	RUCAM
Most frequent HDS (n)	*Camellia sinensis* (7) Herbalife products (5) *Garcinia cambogia* (4)	*Camellia sinensis* (8) Herbalife products (6) *Phyto soya* (3)	Hydroxycut (5) Herbalife products (5) *Camellia sinensis* (4)	Multiple herbals (14) Black cohosh (2) Hydroxycut (2)	Herbal decoction (181) Chitosan Aloe *Camellia sinensis*	Chinese herbal medicine (27)	Red ginseng (6) *Pleuropterus multiflorus* (4)	Herbal decoction with unknown constituents (30) *Radix polygoni multiflora* (3)	Herbal decoction with unknown constituents (33); *Polygonum multiflorum* (6)	*Caulis spatholobi* (11) *Tripterygium wilfordii* (9) *Polygonum multiflorum* (6)	ND

DDW, Digestive Disease Week; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; HILI, herbal and dietary supplements–induced liver injury; ND, no data; RUCAM, Roussel Uclaf Causality Assessment Method.
[a]Standard deviation.
[b]Interquartile range (25th–75th).
[c]Hospital-based study.

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Altogether, the distinct features of HDS hepatotoxicity identified highlight the lack of awareness among the population of the risks of liver injury associated with unsupervised HDS consumption. The current study should contribute to foster the development of pharmacovigilance guidelines for herbal remedies, the search for biomarkers, and specific diagnostic instruments, as well as strategies of prevention and treatment of this type of adverse hepatic reaction.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.01.011.

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Participating clinical centers in the LATINDILI Network and coordinating center in the Spanish DILI Registry are listed in Appendix 1.

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Appendix 1

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Hospital Alemán, CABA: M Anders

Hospital de infecciosas F. J. Muñiz, CABA: M Peralta, S Campuzano, S Paz, H Famboin

Hospital Italiano de La Plata, La Plata: F Gruz

Hospital Universitario Fundación Favaloro: V Descalzi

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Supplementary Table 1. Demographic and Clinical Characteristics of 29 Herbal and Dietary Supplements–Induced Liver Injury Cases Included in the Latin American DILI Network

ID	Botanical name (year of HILI episode)	Brand name	Sex/ Age (*y*)	Purpose for use	Comorbid conditions	Concomitant medication/HDS	Presentation	Hospitalization	Duration, *days*	Latency, *days*	Causality CIOMS/ RUCAM	Comments (positive autoantibodies/ rechallenge)
1	*Camellia sinensis*/ *Gentianella alborosea* (2018)	Green Tea/ Hercampuri	M/59	Weight loss	Metabolic syndrome/pre diabetes mellitus	No	Jaundice	No	44	44	Probable (7)	No
2	*Camellia sinensis* (2015)[a]	Seca Barriga	F/43	Weight loss	Leprosy	Prednisone[b]/ thalidomide[b]/ mirtazapine[b]/ clonazepam[b]/ amitriptyline[b]/ levopromazine[b]	Hypertransaminasemia	No	120	110	Probable (7)	No
3	*Camellia sinensis* (2018)	Hinode Tea	F/38	Weight loss	No	No	Jaundice	Yes	15	7	Probable (7)	ASMA 1/40. Hypersensitivity (fever, arthralgia)
4	*Camellia sinensis* (2018)	Green Tea	F/26	Weight loss	No	No	Jaundice	No	36	29	Probable (8)	
5	*Camellia sinensis*/ *Ginkgo biloba* (2017)	Omnilife	M/18	Energy support	No	No	Jaundice	Yes	175	175	Possible (3)/possible (3)	No
6	*Camellia sinensis*/ Herbalife products (2018)	Green Tea/ Herbalife products	F/68	Weight loss	Dyslipemia	Rosuvastatin[b]	Jaundice	Yes	71/54	68/68	Probable (7)/ probable (6)	No
7	*Camellia sinensis* (2019)	Green Tea	F/37	Weight loss	No	Equisetum arvense,[b] hibiscus[b]	Hypertransaminasemia	No	40	52	Probable (6)	No
8	*Centella asiática* (2014)	Syadel	F/43	Weight loss	No	No	Hypertransaminasemia	Yes	20	25	Possible (5)	No

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Supplementary Table 1. Continued

ID	Botanical name (year of HILI episode)	Brand name	Sex/ Age (*y*)	Purpose for use	Comorbid conditions	Concomitant medication/HDS	Presentation	Hospitalization	Duration, *days*	Latency, *days*	Causality CIOMS/ RUCAM	Comments (positive autoantibodies/ rechallenge)
9	Chitosan/ *Acacia ridigula* (2015)	Chitosan/ Citrux	F/16	Weight loss	ND	Fluoxetine[b]/ levothyroxine[c]	Jaundice	No	29	11	Possible (5)/possible (5)	ASMA 1/10. Hypersensitivity (rash, eosinophilia)
10	Curcumin/ nicotinic acid (2018)	Omnilife/ Dulces sueños	M/34	Anxiety	No	*Matricaria chamomile,*[c] *Melissa Officinalis,*[c] *Sanguisorba minor*[c]	Jaundice	Yes	45	45	Probable (7)	No
11	Echinacea (2012)	Perfectil	F/60	Alopecia	No	No	Hypertransaminasemia	No	16	29	Probable (7)	No
12	*Equisetum arvense*/ rosuvastatin (2014)	ND	M/74	Energy support	Hypertension/ dyslipemia	*Urticaceae,*[c] *Smilax aspera,*[c] *Chenopodium ambrosiodes,*[c] *Targetes Minuta-Asteraceae*[c]	Jaundice	Yes	30	30	Probable (6)	Hypersensitivity (rash)
13	*Garcinia cambogia* (2016)[a]	Lipo On Fire	F/46	Weight loss	No	No	Hypertransaminasemia	No	31	31	Probable (8)	No
14	*Garcinia cambogia* (2014)	Lisopresol	M/16	Weight loss	Metabolic syndrome	No	Jaundice	No	23	23	Possible (5)	No
15	*Garcinia cambogia* (2013)[a]	Lisopresol	F/48	Weight loss	Hypothyroidism	Levothyroxine[c]	Jaundice	No	28	11	Probable (7)	No
16	Herbalife products (2007)[a]	Herbalife products	F/63	Weight loss	Breast cancer without recidive	No	Jaundice	Yes	62	62	Probable (8)	No
17	Herbalife products (2012)[a]	Herbalife products	F/52	Weight loss	Metabolic syndrome/ hypothyroidism/ NAFLD	Metformin[b]/ levothyroxine[b]	Jaundice	Yes	93	94	Probable (7)	INR 2.35
18	Herbalife products (2012)	Herbalife line	M/50	Weight loss	No	Aloe,[c] lemon tea,[c] guarana tea,[c] guarana pills[c]	Hypertransaminasemia	No	338	124	Possible (5)	ANA 1/80. Hypersensitivity (eosinophilia)

Supplementary Table 1. Continued

ID	Botanical name (year of HILI episode)	Brand name	Sex/ Age (*y*)	Purpose for use	Comorbid conditions	Concomitant medication/HDS	Presentation	Hospitalization	Duration, *days*	Latency, *days*	Causality CIOMS/ RUCAM	Comments (positive autoantibodies/ rechallenge)
19[d]	Herbalife products (2007, 2008)[a]	Nutritional Shake	M/43	Energy support	No	No	Jaundice	No	103	94	Highly probable (9)	ANA 1/320. Hypersensitivity (eosinophilia). Rechallenge (2)
20	Hydroxycut (2013)[a]	Hydroxycut	M/48	Weight loss	ND	Alprazolam[b]/ finasteride[b]	Jaundice	No	3	7	Possible (5)	No
21	Kombucha tea (2017)	Kombucha tea	F/70	Probiotic	No	No	Jaundice	No	62	79	Probable (6)	ANA 1/40. ASMA 1/10. AMA 1/10. Hypersensitivity (eosinophilia)
22	*Monascus purpureus* (2012)	Lipistat	M/51	Hyperlipidemia	Dyslipemia/ NAFLD	No	Hypertransaminasemia	No	153	153	Possible (4)	No
23	*Pelargonium sidoides* (2015)[a]	Kaloba	M/18	Acute bronchitis	No	No	Hypertransaminasemia	No	8	9	Probable (7)	No
24	*Peumus boldus* (2007)[a]	Boldo tea	F/23	Urinary tract infection	Allergy	Prednisone[c]/ acetylsalicylic acid[c]/ metamizole[c]/*Piper umbellatum*[c]/*Ruellia bahinensi*[b]	Jaundice	Yes	518	573	Possible (5)	Hypersensitivity (arthralgia, eosinophilia)
25	*Peumus boldus* (2018)	Boldo tea	F/38	Well-being	No	No	Jaundice	No	7	7	Highly probable (10)	Rechallenge
26	Yohimbine/ *Acacia rigidula* (2014)	Lipodex	F/59	Weight loss	No	Amoxicillin-clavulanate[b]	Hypertransaminasemia	No	8	30	Possible (4)	No
27	Yohimbine/ *Acacia rigidula* (2014)[a]	Lipodex	F/27	Weight loss	No	No	Jaundice	Yes	61	76	Possible (4)	ASMA 1/10

Supplementary Table 1. Continued

ID	Botanical name (year of HILI episode)	Brand name	Sex/ Age (*y*)	Purpose for use	Comorbid conditions	Concomitant medication/HDS	Presentation	Hospitalization	Duration, *days*	Latency, *days*	Causality CIOMS/ RUCAM	Comments (positive autoantibodies/ rechallenge)
28	*Croton Cajucara Benth* (1999)[a]	Would Sacaca	F/65	Hypercholestolemia	Hypertension/ dyslipemia	Hydrochlorothiazide[b]	Jaundice	Yes	128	128	Highly probable (10)	Rechallenge
29	Moringa oleífera (2019)	MAX Moringa oleifera	F/60	Dyslipemia	Hypothyroidism, dyslipemia	Ezetimibe,[b] levothyroxine[b]	Hypertransaminasemia	No	28	28	Highly probable (9)	Rechallenge

NOTE. Hypersensitivity features: present one or more positive features as fever, rash, arthralgia, peripheral eosinophilia (eosinophils >4%), or lymphopenia (lymphocytes <10%).
ANA, antinuclear autoantibodies; ASMA, anti-smooth muscular antibodies; HDS, herbal and dietary supplements; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; ND: no data available.
[a]This case was included retrospectively in the Registry.
[b]Concomitant drug or HDS with incompatible time to onset.
[c]Concomitant drug or HDS with compatible or suggestive time to onset.
[d]Published case.

Supplementary Table 2. Clinical and Biochemical Parameters of 29 Herbal and Dietary Supplements–Induced Liver Injury Cases Included in the Latin American Drug-Induced Liver Injury Network

ID	Sex/ Age (*y*)	At HILI episode recognition				Liver damage pattern/ liver biopsy findings (date)	Severity	Outcome (*days*)
		T Bil (*mg/dL*)	AST (× *ULN*)	ALT (× *ULN*)	ALP (× *ULN*)			
1	M/59	7.3	2.8	4.3	0.9	HC	Moderate	Resolved (26)
2	F/43	0.2	5.4	9.3	0.6	HC	Moderate	Resolved (210)
3	F/38	18	27	17	0.5	HC	Moderate	Resolved (120)
4	F/26	3.3	4.9	7.1	2.1	Mix	Moderate	Resolved (15)
5	M/18	20	80	57	3.3	Intracanalicular cholestasis, ductal lesion (1.5 months from DILI recognition)	Moderate	Lost to follow-up (60)[a]
6	F/68	24	19	19	1.4	HC	Severe	ALF recovered (120)
7	F/37	1	7.4	2	0.9	HC	Mild	Resolved (56)
8	F/43	1.1	1.3	2.8	3.2	CHOL	Mild	Resolved (15)
9	F/16	6.4	12	6.8	—	HC	Moderate	Lost to follow-up (30)[a]
10	M/34	8.4	22	23	2.6	Hepatic rosettes, mild fibrosis, ducts injury-inflammatory infiltrate (1.5 months from DILI recognition)	Moderate	Resolved (138)
11	F/60	0.9	3.8	4.3	2.0	Mix	Mild	Resolved (24)
12	M/74	7.4	1.3	5.4	4.1	CHOL	Moderate	Resolved (54)
13	F/46	0.9	38	28	0.5	HC	Mild	Resolved (30)
14	M/16	11	17	51	2.4	HC	Moderate	Resolved (180)
15	F/48	37	9.5	10	1.5	Moderate cholestasis, bridging necrosis (1 month from DILI recognition)	Fatal/liver transplantation	ALF liver transplant (7)[a]
16	F/63	18	14	27	3.2	Cholestasis with hepatitis (ND)	Moderate	Resolved (77)
17	F/52	24	17	10	—	HC	Fatal/liver transplantation	ALF death (7)[a]
18	M/50	0.7	18	52	0.8	Moderate portal hepatitis (2 months from DILI recognition)	Mild	Lost to follow-up (170)[a]
19[b]	M/43	4.3	22	44	1.7	Chronic hepatitis (2 months from DILI recognition)	Moderate	Resolved (49)
20	M/48	11	45	82	1.1	HC	Moderate	Lost to follow-up (54)[a]
21	F/70	15	46	23	1.3	HC	Severe	Lost to follow-up (30)[a]
22	M/51	1	2.9	5.8	0.9	HC	Mild	Resolved (146)
23	M/18	1.5	7.6	12	2.0	HC	Mild	Resolved (31)
24	F/23	7.7	13	19	—	Massive hepatic necrosis	Fatal/liver transplantation	ALF liver transplant (30)[a]
25	F/38	11	36	18	1.6	Cholestasis with hepatitis (1.5 months from DILI recognition)	Moderate	Resolved (150)

Supplementary Table 2. Continued

ID	Sex/ Age (*y*)	At HILI episode recognition: T Bil (*mg/dL*)	AST (× *ULN*)	ALT (× *ULN*)	ALP (× *ULN*)	Liver damage pattern/ liver biopsy findings (date)	Severity	Outcome (*days*)
26	F/59	3	3.4	7.1	2.6	Cholestasis, focal steatosis (3 months from DILI recognition)	Moderate	Lost to follow-up (90)[a]
27	F/27	25	43	44	1.3	HC	Fatal/liver transplantation	ALF death (19)[a]
28	F/65	31	52	65	1.6	HC	Moderate	Resolved (42)
29	F/60	0.6	13	16	1.5	HC	Mild	Resolved (58)

NOTE. Severity index, Mild: elevated ALT/ALP meeting DILI criteria with total bilirubin <2 mg/dL; Moderate: elevated ALT/ALP with total bilirubin ≥2 g/dL; Severe: elevated ALT/ALP and one of the following: ascites, encephalopathy, international normalization ratio >1.5, and/or other organ failure considered to be due to DILI; Fatal: death or transplantation due to DILI. Resolved: normal liver tests.

ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Chol, cholestatic damage; DILI, drug-induced liver injury; HC, hepatocellular damage; HILI, herbal and dietary supplements–induced liver injury; Mix, mixed damage; T Bil, total bilirubin; ULN, upper limit of normal laboratory range.

[a]Days of follow-up.

[b]Published case.