

HERBAL AND DIETARY SUPPLEMENTS-INDUCED LIVER INJURY IN LATIN AMERICA: EXPERIENCE FROM THE 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; AST, aspartate transaminase; BMI, body mass index; CIOMS, Council for International Organizations of Medical Sciences; Chol, cholestatic; DILI, drug induced liver injury; DILIN, Drug-Induced Liver Injury Network; GGT, gamma-glutamyl transpeptidase; HC hepatocellular; HDS, herbal and dietary supplements; HDS-DILI, herbal and dietary supplement induced liver injury; HILI, Herbal induced liver injury; INR, international normalized ratio; LATINDILIN, Latin America DILI Network; Mix, mixed; NAFLD, non-alcoholic fatty liver disease; OTC, over the counter; R, ratio; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

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ABSTRACT

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. Material and 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 ($p=0.04$). *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 ($p=0.008$ and $p=0.021$, respectively), had more re-exposure events to the culprit HDS (14% vs 3% vs 0%; $p=0.026$), and had more severe and fatal/liver transplantation outcome (21% vs 12% vs 13%; $p=0.005$). 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.

Key words: Herbal-induced liver injury, herbal and dietary supplements, drug-induced liver injury, liver toxicity, hepatotoxicity, LATINDILI Network, Latin America.

INTRODUCTION

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 US 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 US 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 over 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 herbs and dietary supplements, there are considerable differences in policies and regulations on traditional medicines.⁹ The main consequence of this heterogeneity is a less regulated market. The WHO 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 LATINDILI network, 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 al¹⁸ 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 as 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 LATINDILI Network and compare this information with results from other series of HDS-related liver injury.

MATERIAL AND METHODS

Cases of HDS-induced liver injury reported to the LATINDILI Network from October 2011 through December 2019 were included in this study. The LATINDILI is a prospective network of countries collecting DILI cases with demographics, clinical, laboratory parameters, imaging, and histological (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 fulfilled 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 centre 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 pharmacological 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 RUCAM scale.

The biochemical DILI criteria used were those defined by an international DILI expert group.¹⁹ The pattern of liver injury were determined using ALT and ALP activity expressed as a multiple of the ULN, to calculate the ratio (R) 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 based on the DILI severity classification¹⁹ 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 chi-squared test. Differences in continuous data were assessed with the Student's t test/ANOVA, or the Mann-Whitney U test/Kruskal-Wallis test, as appropriate. Post hoc analysis with Bonferroni correction for multiple comparisons were performed. Cochran-Armitage's test for linear trend was used to calculate temporal trends in hepatotoxicity cases. In all analyses, a p value<0.05 was considered as statistically significant. All analyses were performed using SPSS version 19.0 (Armonk, NY: IBM Corp).

RESULTS

Characteristics of HDS related liver injury cases reported to the LATINDILI Network

From a total of 367 DILI cases included in the Latin-American DILI Network 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%), 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 ($p=0.0435$). (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 (38%) cases were induced by single ingredient products while 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 most cases (9), followed by Brazil (7 cases), and Peru (5 cases).

Patient mean age was 45 years and 66% were females. The median time to onset was 31 days. The most common reason for consultation was jaundice, in 19 (68%) patients, and hepatocellular was the most common pattern of liver injury (24 cases, 83%) (Supplementary table 1).

In terms of severity and outcome, 12 patients required hospitalization (41%) and 5 cases due to *Camellia sinensis*/Herbalife® products, *Garcinia cambogia*, Herbalife® products, *Peumus boldus*, and *Yohimbin/Acacia rigidula* developed ALF (17%), of whom two underwent liver transplantation, two died and one resolved spontaneously. Twelve cases (41%) fulfilled nR-based Hy's law criteria. Although follow-up was lost in 6 patients prior to 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).

HDS-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 three groups ($p<0.001$), with older HILI and DILI patients (45 and 50 years old, respectively) compared to AAS patients (31 years old) (Table 1). Females were similarly represented in HILI and DILI cases (66% vs 64%), while there was just one 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 due to HDS had the highest mean values of aminotransferases and had significantly higher values of bilirubin compared to DILI cases ($p=0.043$). 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 due to 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) ($p=0.026$). Liver biopsy was performed in 31% (9 cases) of the HDS 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%; $p=0.005$). Four AAS-related DILI cases (25%) developed acute renal dysfunction compared with two cases (6.9%) due to HDS and 22 (6.8%) related to drugs ($p=0.045$).

Comparison with other HDS hepatotoxicity series

Frequency of HDS hepatotoxicity was higher in the Latin American Registry compared to the Spanish DILI (4%). Nonetheless, when compared to other prospective DILI registries (US 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 LATINDILI Network (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 which 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 US DILIN (16%), but higher compared to the Spanish DILI Registry (6%) and

retrospective registries (China 7.6% and Korea 1.4%), and lower when compared to Pakistani cases (26%).

DISCUSSION

Herbal and dietary supplements-induced liver injury is a growing concern worldwide. Epidemiological and clinical information of hepatotoxicity associated with these products in Latin America, however, is very limited. The prospective LATINDILI network encompasses seven Latin-American countries, which have similarities but also differences with regards to, prescription patterns, traditional medicine market, and regulatory policies.^{16,17} The twenty-nine prospectively collected liver injury cases attributed to HDS in the LATINDILI Network (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 products and/or increased case detection due to 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 US 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 (OTC) 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 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, two of the patients with positive autoantibodies underwent a liver biopsy. Case 19 (due to Herbalife® products), with high titers of antinuclear antibodies (1/320) and features of chronic hepatitis in the liver biopsy, had a positive re-challenge, 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 one 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 herbal and dietary supplements such as *Polygonum multiflorum*²⁸ or Herbalife® products²⁹, 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 CIOMS/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 admission (41%) compared to those observed in Spanish and US HILI series (63% and 68%, respectively).^{4,7} These results could be attributed to differences in healthcare 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 acute liver failure or death and included in prognostic models.^{20,32} Evermore, 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 that precludes detecting geographical and clinical differences between the countries included in the LATINDILI Network. Nevertheless, this is the first prospective collection of hepatotoxicity cases 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.

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.

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Author names in bold designate shared co-first authorship.

Table 1. Demographics, clinical and laboratory characteristics in 367 Latin-American hepatotoxicity cases induced by herbal and dietary supplements (HDS), conventional medicines, and anabolic androgenic steroids (AAS).

	HDS (n=29)	Conventional medicines (n=322)	AAS (n=16)	p value
Age, years (mean; range)	45 (16-74)	50 (14-89)	31 (20-47) ^{b,c}	<0.001
Female, n (%)	19 (66)	207 (64)	1 (6.3) ^{b,c}	<0.001
BMI, kg/m ² (median; IQR)	24 (23-28)	25 (23-28)	24 (23-26)	0.838
<i>Clinical presentation</i>				
Jaundice, n (%)	19 (66)	194 (61)	14 (88) ^c	0.074
Hospital admission, n (%)	12 (41)	140 (44)	9 (56)	0.607
Duration of treatment, days (median; IQR)	41 (23-93)	31 (11-83)	59 (41-128) ^c	0.018
Time to DILI onset, days (median; IQR)	31 (24-66)	29 (11-68)	62 (37-94)	0.117
Type of liver injury, n (%)				0.046
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)	0.097
<i>Renal dysfunction</i>				
Hepatocellular	2 (6.9)	22 (6.8)	4 (25) ^c	0.045
Cholestatic/mixed	0 (0)	9 (41)	3 (75)	0.329
Hepatocellular total bilirubin, mg/dl (mean; IQR)	0.9 (0.9-1.0)	5.0 (2.0-7.8)	8.7	0.309
Cholestatic/mixed total bilirubin, mg/dl (mean; IQR)	NA	4.5 (2.1-4.9)	5.7 (4.2-7.5)	0.195
<i>Laboratory parameters at onset (mean; IQR)</i>				
Total bilirubin, mg/dL	9.7 (1.0-17)	6.4 (1.0-8.5)	11 (5.9-15) ^c	0.001
AST, x ULN	19 (5.1-25)	14 (3.0-18)	8.6 (2.0-7.8) ^{b,c}	0.008
ALT, x ULN	22 (6.8-28)	16 (4.8-20)	13 (2.5-11) ^b	0.021
GGT, x ULN	6.6 (1.6-10)	10 (3.4-12)	3.9 (1.6-6.5) ^c	0.022
ALP, x ULN	1.8 (0.9-2.6)	2.4 (1.1-3.0)	1.4 (0.5-2.6) ^c	0.029
<i>Outcome</i>				
Liver transplant, n (%)	2 (6.9)	8 (2.5)	0 (0)	0.240
Death, n (%)	2 (6.9)	6 (1.9)	1 (6.3)	0.112
Time to resolution, days (median; IQR)	54 (30-120)	67 (36-130)	90 (90-120)	0.100
Rechallenge, n (%)	4 (14)	8 (2.5) ^a	0 (0)	0.026
Severity, n (%)				0.005
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)	

HDS: herbal and dietary supplements; AAS: anabolic androgenic steroids; IQR: interquartile range; Tx: liver transplantation. Renal dysfunction was defined as serum creatinine (SCr) values ≥ 1.5 mg/dL in patients with no pre-existing kidney damage.

^a p<0.05 HDS vs conventional medicines

^b p<0.05 HDS vs AAS

^c p<0.05 AAS vs conventional medicines

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 ³⁴	Korea ³⁵	Beijing, China ³⁶	Beijing, China ¹²	Shanghai, China ³⁷	Pakistan ³⁸
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, mean (range)	45 (16-74)	48 (18-78)	47 (38,61) [#] (median)	41 (median)	51 (18-79) (median)	59 (30-79) (median)	ND	45±13*	43 ± 14*	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) [‡]	270 (100) [‡]	ND	28 (100) [‡]	488 (100) [‡]	563 (100) [‡]	111 (100) [‡]	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)
Re-challenge, n (%)	4 (14)	3 (9)	ND	ND	ND	ND	ND	35 (7.2)	50 (8.9)	ND	ND
Causality assesment	RUCAM	RUCAM	DILIN Expert Opinion	DILIN Expert Opinion	RUCAM	DDW-J 2004 score and RUCAM	RUCAM	RUCAM	RUCAM	RUCAM	RUCAM
Most frequent HDS (n)	<i>Camellia sinensis</i> (7) Herbalife products (5) <i>Garcinia cambogia</i> (4)	<i>Camellia sinensis</i> (8) Herbalife products (6) <i>Phyto soya</i> (3)	Hydroxycut (5) Herbalife products (5) <i>Camellia sinensis</i> (4)	Multiple herbals (14) Black cohosh (2) Hydroxycut (2)	Herbal decoction (181) Chitosan Aloe <i>Camellia sinensis</i>	Chinese herbal medicine (27)	Red ginseng (6) <i>Pleuropterus multiflorus</i> (4)	Herbal decoction with unknown constituents (30) <i>Radix polygoni multiflora</i> (3)	Herbal decoction with unknown constituents (33); <i>Polygonum multiflorum</i> (6)	<i>Caulis spatholobi</i> (11) <i>Tripterygium wilfordii</i> (9) <i>Polygonum multiflorum</i> (6)	ND

*SD; # IQR (25th, 75th); † Hospital-based study. Abbreviations: HILI, herbal and dietary supplements-induced liver injury; DDW, Digestive Disease Week; ND, no data; RUCAM, Roussel Uclaf Causality Assessment Method.

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	Purpose for use	Comorbid conditions	Concomitant medication/HDS	Presentation	Hospitalization	Duration Days	Latency days	Causality CIOMS/RUCAM	Comments (Positive autoantibodies/Rechallenge)
1	<i>Camellia sinensis/Gentianella alborosea</i> (2018)	Green Tea/Hercampuri	M/59	weight loss	metabolic syndrome/ pre DM	No	Jaundice	No	44	44	Probable (7)	No
2	<i>Camellia sinensis</i> (2015)*	Seca Barriga	F/43	weight loss	leprosy	prednisone [#] / thalidomide [#] / mirtazapine [#] / clonazepam [#] / amitriptyline [#] / levopromazine [#]	Hypertransaminasemia	No	120	110	Probable (7)	No
3	<i>Camellia sinensis</i> (2018)	Hinode Tea	F/38	weight loss	No	No	Jaundice	Yes	15	7	Probable (7)	ASMA 1/40. Hypersensitivity (fever, arthralgia)
4	<i>Camellia sinensis</i> (2018)	Green Tea	F/26	weight loss	No	No	Jaundice	No	36	29	Probable (8)	
5	<i>Camellia sinensis/Ginkgo biloba</i> (2017)	Omnilife	M/18	energy support	No	No	Jaundice	Yes	175	175	Possible (3)/ Possible (3)	No
6	<i>Camellia sinensis/Herbalife</i> ® products (2018)	Green Tea/Herbalife products	F/68	weight loss	dyslipemia	rosuvastatin [#]	Jaundice	Yes	71/54	68/68	Probable (7)/ Probable (6)	No
7	<i>Camellia sinensis</i> (2019)	Green Tea	F/37	weight loss	No	Equisetum arvense [#] ,	Hypertransaminasemia	No	40	52	Probable (6)	No

						hibiscus [‡]						
8	<i>Centella asiática</i> (2014)	Syadel	F/43	weight loss	No	No	Hypertransam inasemia	Yes	20	25	Possible (5)	No
9	Chitosan/ <i>Acacia ridigula</i> (2015)	Chitosan/ Citrux	F/16	weight loss	ND	fluoxetine ⁺ / levothyroxine ⁺	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	<i>Matricaria chamomile</i> ⁺ , <i>Melissa Officinalis</i> ⁺ and <i>Sanguisorba minor</i> ⁺	Jaundice	Yes	45	45	Probable (7)	No
11	Echinacea (2012)	Perfectil	F/60	alopecia	No	No	Hypertransam inasemia	No	16	29	Probable (7)	No
12	<i>Equisetum arvense</i> /rosuvastatin (2014)	ND	M/74	energy support	hypertension/ dyslipemia	<i>Urticaceae</i> ⁺ , <i>Smilax aspera</i> ⁺ , <i>Chenopodium ambrosiodes</i> ⁺ and <i>Targetes Minuta-Asteraceae</i> ⁺	Jaundice	Yes	30	30	Probable (6)	Hypersensitivity (rash)
13	<i>Garcinia cambogia</i> (2016)*	Lipo On Fire	F/46	weight loss	No	No	Hypertransam inasemia	No	31	31	Probable (8)	No
14	<i>Garcinia cambogia</i> (2014)	Lisopresol	M/16	weight loss	metabolic syndrome	No	Jaundice	No	23	23	Possible (5)	No
15	<i>Garcinia cambogia</i> (2013)*	Lisopresol	F/48	weight loss	hypothyroidism	levothyroxine [‡]	Jaundice	No	28	11	Probable (7)	No
16	Herbalife products (2007)*	Herbalife products	F/63	weight loss	breast cancer without recidive	No	Jaundice	Yes	62	62	Probable (8)	No
17	Herbalife products (2012)*	Herbalife products	F/52	weight loss	metabolic syndrome/ hypothyroidism/ NAFLD	metformin [‡] / levothyroxine [‡]	Jaundice	Yes	93	94	Probable (7)	INR:2.35

18	Herbalife products (2012)	Herbalife line	M/50	weight loss	No	Aloe ⁺ , lemon tea ⁺ , guarana tea ⁺ and guarana pills ⁺	Hypertransaminasemia	No	338	124	Possible (5)	ANA 1/80. Hypersensitivity (eosinophilia)
19 ^a	Herbalife® products (2007, 2008)*	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)*	Hydroxycut	M/48	weight loss	ND	alprazolam [#] /finasteride [#]	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	<i>Monascus purpureus</i> (2012)	Lipostat	M/51	hyperlipidemia	dyslipemia/NAFLD	No	Hypertransaminasemia	No	153	153	Possible (4)	No
23	<i>Pelargonium sidoides</i> (2015)*	Kaloba	M/18	acute bronchitis	No	No	Hypertransaminasemia	No	8	9	Probable (7)	No
24	<i>Peumus boldus</i> (2007)*	Boldo tea	F/23	urinary tract infection	allergy	prednisone ⁺ /acetylsalicylic acid ⁺ /metamizole ⁺ / <i>Piper umbellatum</i> ⁺ / <i>Ruellia bahinensis</i> [#]	Jaundice	Yes	518	573	Possible (5)	Hypersensitivity (arthralgia, eosinophilia)
25	<i>Peumus boldus</i> (2018)	Boldo tea	F/38	Well-being	No	No	Jaundice	No	7	7	Highly probable (10)	Rechallenge
26	Yohimbin/ <i>Acacia rigidula</i> (2014)	Lipodex	F/59	weight loss	No	amoxicillin-clavulanate [#]	Hypertransaminasemia	No	8	30	Possible (4)	No
27	Yohimbin/ <i>Acacia rigidula</i> (2014)*	Lipodex	F/27	weight loss	No	No	Jaundice	Yes	61	76	Possible (4)	ASMA 1/10

28	<i>Croton Cajucara Benth</i> (1999)*	Would Sacaca	F/65	hypercholesterolemia	hypertension/dyslipemia	Hydrochlorothiazide [‡]	Jaundice	Yes	128	128	Highly probable (10)	Rechallenge
29	<i>Moringa oleifera</i> (2019)	MAX Moringa oleifera	F/60	dyslipemia	hypothyroidism, dyslipemia	ezetimibe [‡] , levothyroxine [‡]	Hypertransaminasemia	No	28	28	Highly probable (9)	Rechallenge

*This case was included retrospectively in the Registry. [‡]Concomitant drug or HDS with incompatible time to onset. [†]Concomitant drug or HDS with compatible or suggestive time to onset. [^]Published case. Hypersensitivity features: present one or more positive features as fever, rash, arthralgia, peripheral eosinophilia (eosinophils >4%), or lymphopenia (lymphocytes <10%). Abbreviations: ANA, antinuclear autoantibodies; ASMA, anti-smooth muscular antibodies; NAFLD, non-alcoholic fatty liver disease; ND: no data available.

Supplementary Table 2. Clinical and biochemical parameters of 29 herbal and dietary supplements induced liver injury (HILI) cases included in the Latin-American DILI Network.

ID	Sex/Age	At HILI episode recognition				Liver damage pattern/ Liver biopsy findings (date)
		T Bil (mg/dL)	AST (x ULN)	ALT (x ULN)	ALP (x ULN)	
1	M/59	7.3	2.8	4.3	0.9	HC
2	F/43	0.2	5.4	9.3	0.6	HC
3	F/38	18	27	17	0.5	HC
4	F/26	3.3	4.9	7.1	2.1	MIX
5	M/18	20	80	57	3.3	Intracanalicular cholestasis, ductal lesion (1.5 months from DILI recognition)
6	F/68	24	19	19	1.4	HC
7	F/37	1	7.4	2	0.9	HC
8	F/43	1.1	1.3	2.8	3.2	CHOL
9	F/16	6.4	12	6.8	-	HC
10	M/34	8.4	22	23	2.6	Hepatic rosettes, mild fibrosis, ducts injury-inflammatory infiltrate (1.5 months from DILI recognition)
11	F/60	0.9	3.8	4.3	2.0	MIX
12	M/74	7.4	1.3	5.4	4.1	CHOL
13	F/46	0.9	38	28	0.5	HC
14	M/16	11	17	51	2.4	HC
15	F/48	37	9.5	10	1.5	Moderate cholestasis, bridging necrosis (1 month from DILI recognition)
16	F/63	18	14	27	3.2	Cholestasis with hepatitis (ND)
17	F/52	24	17	10	-	HC
18	M/50	0.7	18	52	0.8	Moderate Portal hepatitis (2 months from DILI recognition)
19 [^]	M/43	4.3	22	44	1.7	Chronic hepatitis (2 months from DILI recognition)
20	M/48	11	45	82	1.1	HC
21	F/70	15	46	23	1.3	HC
22	M/51	1	2.9	5.8	0.9	HC
23	M/18	1.5	7.6	12	2.0	HC

24	F/23	7.7	13	19	-	Massive hepatic necrosis
25	F/38	11	36	18	1.6	Cholestasis with hepatitis (1.5 months from DILI recognition)
26	F/59	3	3.4	7.1	2.6	Cholestasis, focal steatosis (3 months from DILI recognition)
27	F/27	25	43	44	1.3	HC
28	F/65	31	52	65	1.6	HC
29	F/60	0,6	13	16	1,5	HC

*days of follow-up. ^Published case. Abbreviations: T Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HILI, Herb & Dietary supplements induced liver injury; ALF, acute liver failure; Chol, cholestatic damage; HC, hepatocellular damage; Mix, mixed damage; F, female; M, male; ULN, upper limit of normal laboratory range. 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.

LEGEND TO FIGURES

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: 0.0435; p for trend for DILI: 0.0696; p for trend AAS-DILI: 0.8045

HILI: herbal & Dietary supplements-induced liver injury; DILI: Drug-Induced Liver Injury; AAS: anabolic and androgenic steroids

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

T Bil: total bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.

Figure 1.

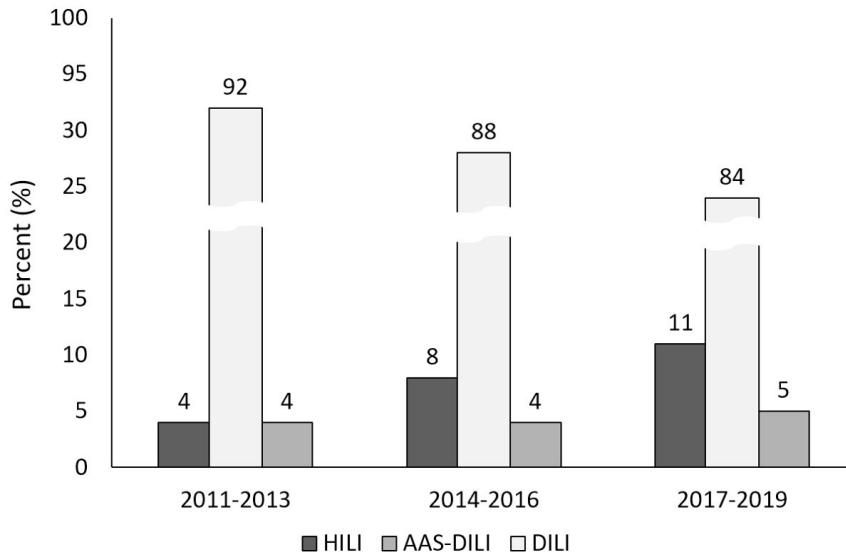


Figure 2.

