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REVIEW

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Profile of herbal and dietary supplements induced liver injury in Latin America: A systematic review of published reports

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Hepatotoxicity related to HDS is a growing global health issue. We have undertaken a systematic review of published case reports and case series from LA from 1976 to 2020 to describe the clinical features of HDS related hepatotoxicity in this region. We search in PubMed, Web of Science, Scopus and specific LA databases according to PRISMA guidelines. Only HILI cases published in LA that met criteria for DILI definition were included. Duplicate records or reports that lacked relevant data that precluded establishing causality were excluded. Finally, 17 records (23 cases) were included in this review. *Centella asiatica*, *Carthamus tinctorius*, and Herbalife® were the most reported HDS culprit products, the main reason for HDS consumption was weight loss. The clinical characteristics of HDS hepatotoxicity in our study were compared to those of other studies in the USA, Europe and China showing a similar signature with predominance of young females, hepatocellular damage, a high rate of ALF and mortality, more frequent inadvertent re-challenge and chronic damage. This study underscores the challenge in causality assessment when multi-ingredients HDS are taken and the need for consistent publication practice when reporting hepatotoxicity cases due to HDS, to foster HDS liver safety particularly in LA.

KEYWORDS
hepatotoxicity, herbal and dietary supplements-induced liver injury, Latin America, outcome, phenotypic presentations

1 | INTRODUCTION

The use of natural products for therapeutic purposes is a common practice worldwide. In Europe there is a growing use of herbal products mainly for "improving or maintaining health" that has been estimated to reach 19% of adult population (Garcia-Alvarez et al., 2014). However, in LA there is a large market for herbal and dietary supplements (HDS) as an important side of folk medicine, since these products are more accessible and affordable (Andrade, Medina-Caliz, Gonzalez-Jimenez, Garcia-Cortes, & Lucena, 2018). The worldwide herbal medicine market was estimated to approximately US $107 billion in 2017 (Global Industry Analysts, 2017) and is forecasted to reach US $140 billion in 2024 (Global Industry Analysts, 2019). Brazil represents 34% of the suppliers of the active ingredients in the herbal medicine market and the Brazilian market turnaround is estimated to be US $400 million, representing 12% increase per year, which is higher than that of conventional drugs that are expected to have an annual increase of approximately 5% (Carvalho, Lana, Perfeito, & Silveira, 2018; Castro & Albiero, 2016; Tabajara de Oliveira Martins, Rodrigues, Casu, Benítez, & Leonti, 2019).

The term HDS encompasses a broad spectrum of products, including herbs, herbal preparations, food supplements, vitamins,

Genario Santos and Jessica Gasca contributed equally to this work.

and minerals (Navarro & Lucena, 2014). Although these substances are often assumed to be natural and safe, information on safety concerns is controversial due to lack of scientific efficacy and toxicity data (Morris & Avorn, 2003). Hence, some of these products have been associated with liver injury and more than 120 HDS implicated in liver toxicity have been reported to date (Navarro et al., 2014; Seeff, Bonkovsky, Navarro, & Wang, 2015). However, there are other factors such as product contamination (obtaining and processing time) and addition of substances that are omitted from the label information that could be involved in the development of hepatotoxicity (Stedman, 2002). Less than 10% of the herbal products are truly standardized and adhere to strict quality control measures (Ifeoma & Oluwakanyinsol, 2013). Because of this, regulation of herbal remedies is essential to ensure quality, safety and efficacy. There are currently considerable differences in the kind of policies and regulations on production and post-marketing monitoring of HDS among different Latin American countries, representing the most heterogeneous and less regulated market in the world (Andrade et al., 2018). The WHO Traditional Medicine Strategy 2014–2023 is expected to help strengthen regulatory frameworks and safety monitoring in LA (World Health Organization, 2019. WHO Traditional Medicine Strategy: 2014–2023).

Due to the growing use of herbal products and herbal medicines worldwide, liver safety is an important public health issue particularly in LA with high biodiversity and cultural behaviors. Mexico has the largest number of herbs in LA with approximately 4,500 recorded species (Valdivia-Correa, Gómez-Gutiérrez, Uribe, & Méndez-Sánchez, 2016) just behind China that ranks first in the world with more than 5,000 species (Liu, Fan, Li, & Xiao, 2016).

In general, the real incidence of HDS-induced liver injury (HILI) remains unknown. Recent efforts across the world in population-based studies or prospectively collecting cases of hepatotoxicity have started to provide some figures on the incidence and relative prevalence of HDS induced liver injury compared to conventional drugs. According to the US Drug-Induced Liver Injury Network (DILIN), the annual incidence of drug- and herbal and dietary supplement hepatotoxicity is estimated at 2.7 cases per 100,000 adults in 2014 with 43% of the incident cases being attributed to HDS (Vega et al., 2017), an extrapolated HDS incidence of three cases per 100,000 inhabitants in Iceland (Björnsson, Bergmann, Björnsson, & Kvaran, 2013), while Suk et al. (2012) reported figures of DILI and HILI hospitalized cases of 12/100,000 habitants per year between 2004 and 2007 in South Korea. A recent three-year retrospective multicenter study from Mainland China reported an average incidence of DILI and HILI in the general population of 23.80 per 100,000 persons (Shen et al., 2019). A study published by the Spanish DILI group, showed that 6% of the hepatotoxicity cases were related to HDS, while in the US DILIN the figures reached 14% during 2013–2014 (Medina-Caliz et al., 2018; Navarro et al., 2014). In the LATIN DILI Network, it is estimated that HDS hepatotoxicity represents 10% of the causes of acute liver injury (Bessone, Hernandez, Lucena, & Andrade, 2016) although the characteristics of HDS hepatotoxicity in LA have not yet been published in detail (Byeon, Kil, Ahn, & Son, 2019).

Up to date the reports of HDS hepatotoxicity published in scientific journals are the only epidemiological information available in LA. Hence, we aimed to systematically review published case reports and case series of HDS-induced liver injury in LA in order to identify the species more frequently involved and the clinical phenotype and outcome of this variety of hepatotoxicity in Latin American countries over a 44-year time period.

2 | MATERIAL AND METHODS

2.1 | Systematic search strategy

A systematic literature search was performed in PubMed, Web of Science and Scopus and specific LA databases (Lilacs and Scielo), to identify any case reports and case series of published HILI from 1976 to 2020, according to "Preferred Reporting Items of Systematic Reviews and Meta-Analysis" (PRISMA) guidelines. We searched the following terms in the title and abstract: "hepatotoxicity" OR "acute liver injury" OR "liver injury" OR "liver damage" OR "acute liver failure" OR "cholestasis" AND "herbal medicine" OR "herbs" OR "dietary supplements" OR "phytotherapy" OR "complementary therapies". There were no language or article type restrictions. References from selected manuscripts were also searched to identify other eligible studies. Two independent researchers (GS and JG) conducted the search and evaluated the studies. In case of discrepancies between these two authors, a third researcher (MIL) was consulted.

2.2 | Eligibility criteria

The criteria for DILI definition according to Bénichou (1990) and Aithal et al. (2011) were used to assess eligibility of the published cases. To make a reliable assessment of the cases with liver injury we searched for a detailed clinical history, the presence of a temporal relationship between the prescription of the suspected drug and the onset of liver injury and between the withdrawal of the drug and the improvement of the disease; an exclusion of alternative causes of liver damage; and the outcome of the reaction. A previous knowledge of the potential for hepatotoxicity of the herb or dietary supplement was searched for. Only cases published in LA countries and with sufficient information to establish causality were included in the analysis. Duplicate records, reports that did not meet the eligibility criteria and lacking relevant description data that precluded establishing causality were excluded from the analysis.

2.3 | Data collection

Two independent researchers (G. S. and J. G.) conducted the data extraction, resolving the differences by consulting a senior researcher (M. I. L.). The following data were retrieved and analyzed from each article identified in the literature search: country source of the report,

demographics, suspected HDS or herbal compounds, type of liver injury, biochemical parameters, histological findings, and outcome of the reaction.

Chronicity was defined according to Medina-Caliz et al. (2016) as abnormal liver biochemistry, imaging test or histology 1 year after DILI recognition.

3 | RESULTS

A systematic literature review was conducted in accordance with the "Preferred Reporting Items of Systematic Reviews and Meta-Analysis" (PRISMA) guidelines, in order to identify all studies on HDS-induced liver injury published in LA to date (Figure 1). A total of 13,904 records were identified on the initial database search. After excluding 3,590 duplicate records, and 9,485 that did not fulfill the eligibility criteria, 19 records were screened. We excluded two records due to due to lacking relevant description data that precluded establishing causality (Ramirez Rodriguez, Pabón Uego, Ortiz, Duchen, & Ávila, 2004; Restrepo et al., 2008). Finally, 17 records were included in the narrative review.

Twenty-three HDS hepatotoxicity cases published from January 1976 to February 2020 in LA countries including Argentina (seven cases), Brazil (eight cases), Colombia (two cases), Ecuador (one case), Mexico (two cases), Puerto Rico (one case) and Venezuela (two cases) were found. Table 1 summarizes demographic and clinical characteristics of the cases included in the current study. A higher proportion of patients were females (87%), mean age 44 years (range 2–79 years). Twelve (52%) of the cases were induced by single ingredient compounds and 11 (48%) by multi-ingredient products. *Centella asiatica* was the herb most involved (20%) among the single ingredient products and Herbalife® products, in published cases between 2007 and 2013, and *Carthamus tinctorius* were the most frequently reported (48% and 27%) multi-ingredient products.

The most frequent indication for the intake of HDS products was weight loss in 12 cases (52%). In the remaining patients, the HDS products were used to relieve symptoms of digestive disorders, constipation, hair loss, arthralgia, diabetic neuropathy, anxiety and to maintain overall health. Median duration of treatment in the HDS cases was 111 days (21–365 days) and the median latency period between HDS consumption and the start of symptoms was 81 days (21–225 days). The most frequent sign for which patients sought medical consultation was jaundice (48%). In six cases (26%) comorbidities such as arthralgia (Case 8), hypothyroidism (Cases 9, 15, and 17), limited systemic sclerosis (Case 9), morbid obesity (Case 10), HIV infection (case 11), arterial hypertension, diabetes mellitus or chronic renal failure (Case 17) were present (Table 1). Co-medications were used in seven cases. Long-term therapy was used in four cases, including levothyroxine and nifedipine (case 9); insulin, valsartan and levothyroxine (Case 17); levonorgestrel and ethinyl estradiol (Case 18); and omeprazole (Case 23). In Case 18, other herbal medicines (*Peumus boldus* and *Piper umbellatum*) were used at the same time of culprit

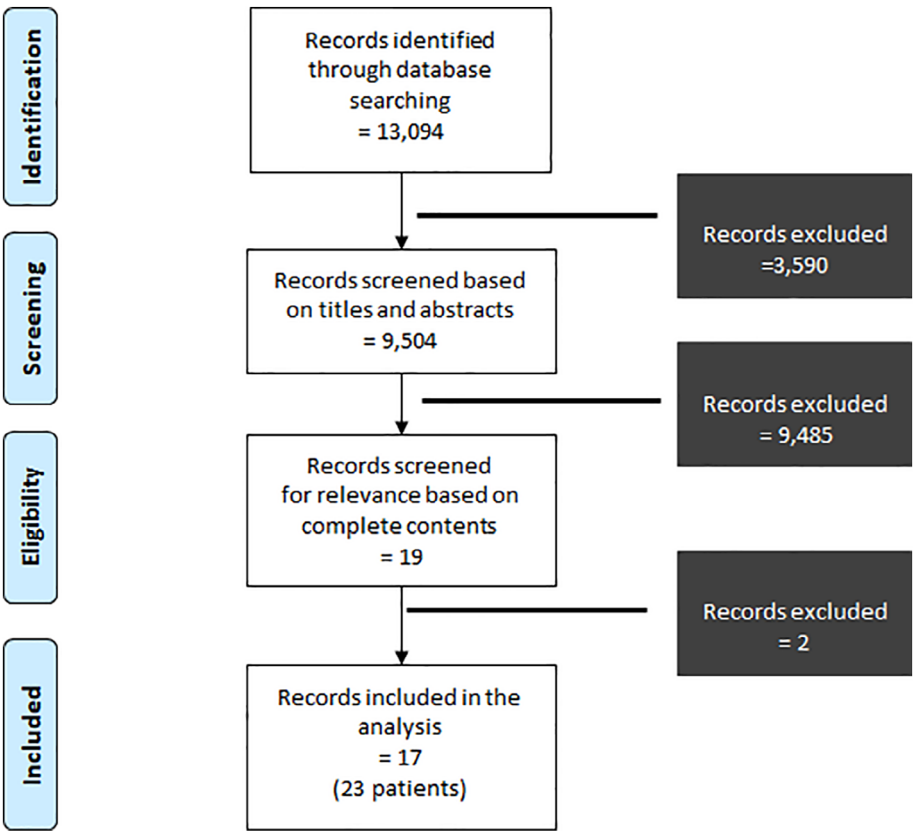

FIGURE 1 Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Demographic and Clinical Characteristics in 23 published cases of Herbal and Dietary Supplements induced liver injury in Latin American

Patient no.	Botanical brand name	Age/ gender	Treatment duration (days)	Time to onset (days)	Indication use	Dose (daily)	Clinical presentation	Co-medications	Causality assessment	Country/Ref.
01	*Aloe vera*	26/M	72	30	Digestive Disorders	Infusion of herbs	Jaundice	None	CIOMS Probable	Argentina/(Curciarello, De Ortúzar, & Borzi, 2008)
02	*Argemone mexicana* L.	55/F	NA	NA	Digestive disorders	NA	Jaundice Rechallenge	None	CIOMS Highly probable	Mexico/(Meléndez González, 2013)
03	*Camellia sinensis*	43/F	240	225	Constipation	Infusion of herbs	Abdominal pain Fever	None	Karch-Lasagna: Problabe	Colombia/(Muñoz, Angulo, Agudelo-Agudelo, & Gaviria, 2009)
04	*Centella asiatica*	61/F	30	30	Weight loss	Tablets unknown strength	Jaundice Choluria Hepatomegaly Arthralgia Hepatomegaly Rechallenge	None	NA	Argentina (Jorge & Jorge, 2005)
05	*Centella asiatica*	52/F	21	21	Weight loss	Tablets	Jaundice Choluria Hepatomegaly Rechallenge	None	NA	Argentina/(Jorge & Jorge, 2005)
06	*Centella asiatica*	49/F	60	60	Weight loss	Tablets	Jaundice Asthenia Hepatomegaly	None	NA	Argentina/(Jorge & Jorge, 2005)
07	*Cochlospermum vitifolium*	25/F	120	120	Maintain Overall health	Infusion of herbs 500 mL	Jaundice	None	CIOMS Probable	Mexico/(Martínez-Rodriguez, Murguía-Hernández, García-Juárez, Uribe-Esquivel, & Gómez-Reyesa, 2015)
08	*Crotalaria juncea*	35/F	120	210	Arthralgia	2 L	Abdominal pain, ascites Portal hypertension Cirrhosis Pregnancy at the time of HILI diagnosis	None	NA	Ecuador/(Lyford, Vergara, & Moeller, 1976)
09	Euforia®	45/F	NA	30	Weight loss	60 mL of juice	Jaundice Fever	Levothyroxine Nifedipine	CIOMS Probable	Puerto Rico/(Jiménez-Encarnación, Ríos, Muñoz-mirabal, & Vilá, 2012)
10	Herbalife® used in 2013	52/F	30	NA	Weight loss	NA	NA	NA	CIOMS Probable	Venezuela/(Mengual-Moreno et al., 2015)
11	Herbalife® used in 2013	36/F	90	NA	Weight loss	NA	NA	NA	CIOMS Possible	Venezuela/(Mengual-Moreno et al., 2015)

TABLE 1 (Continued)

Patient no.	Botanical brand name	Age/ gender	Treatment duration (days)	Time to onset (days)	Indication use	Dose (daily)	Clinical presentation	Co-medications	Causality assessment	Country/Ref.
12	Herbalife® used in 2013	42/F	90	90	Weight loss	NA	Asthenia Dizziness	30 ervas® tea 6-Months before starting Herbalife® products use	CIOMS Highly probable	Brazil/(Ferreira Rios et al., 2016)
13	Herbalife® used in 2013	54/F	365	NA	Weight loss	NA	Fever Abdonimal pain	30 ervas® tea Concomitantly	CIOMS Possible	Brazil/(Ferreira Rios et al., 2016)
14	Herbalife® used in 2007	63/F	70	40	Weight loss	70 g 02 tablets	Jaundice	Nutritional shake mix formula 1, personal protein powder	WHO Probable	Argentina/(Chao et al., 2008)
15	*Hypericum perforatum*	79/F	NA	NA	NA	NA	Jaundice	*Copaifera langsdorfii Desf* Levothyroxine Ômega 3 Glucosamine Condroitin	NA	Brazil/(Agollo Costa, Jankiel Miszputen, & Diament, 2014)
16	Shen-Min®	28/F	56	51	Hair supplement	2 tablets	Jaundice Hepatomegaly	None	CIOMS Probable	Colombia/(Cárdenas, Restrepo, Sierra, & Correa, 2006)
17	Tiodrix HR®	63/M	49	45	Diabetic neuropathy	Tablets 600 mg	Fever Pruritus Rechallenge	Insulin Valsartan levothyroxine	CIOMS Highly probable	Argentina/(Ridruejo, Castiglioni, & Silva, 2011)
18	*Ruellia bahiensis*	23/F	150	150	Digestive disorders	Infusion of herbs	Abdominal pain	Levonogestrel, Ethinily estradiol, prednisone, *Peumus boldus, Piper umberllatum*	Teschke, Schwarzenboeck and Hennermann's algorithm Possible	Brazil/(Santos Júnior, Ferreira Filho, Codes Foulon, & Beisl Noblat, 2018)
19	*Camellia sinensis*	2/M	150	150	Digestive disorders—substitute for milk	Infusion of herbs	NA	Amoxicillin for 7 days, 1 month before hospitalization	NA	Argentina/(D'Agostino, Cavalieri, & Arcucci, 2019)
20	*Carthamus tinctorius*	44/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/(de Ataide et al., 2018)
21	*Carthamus tinctorius*	66/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/(de Ataide et al., 2018)
22	*Carthamus tinctorius*	32/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/(de Ataide et al., 2018)

(Continues)

TABLE 1 (Continued)

Patient no.	Botanical brand name	Age/gender	Treatment duration (days)	Time to onset (days)	Indication use	Dose (daily)	Clinical presentation	Co-medications	Causality assessment	Country/Ref.
23	*Piper methysticum*	45/F	52	52	Anxiety	Capsules	Jaundice	Omeprazole for 4 years Bromazepam for 2 years (stop using Bromazepam and start to use the herb)	RUCAM Probable	Brazil/(Becker et al., 2019)

Note: Euforia®: Acai berry, Mangosteen, Aloe vera, Resveratrol cucumin, *Nigella sativa*, Blueberry pomegranate, Green tea, *Morinda citrifolia* (Noni) Goji berry. Shen-Min®: Polygonum mutiflorum, *Cimicifuga racemosa*, *Piper nigrum*, Black cohosh, *Ginkgo biloba*, He Shou Wu, Burdock, Cayenne pepper, Vitamin A Vitamin B-6, Biotin Niacin Pantothenic acid, Soy isoflavones, Horse chestnut, Hydrolyzed collagen, Silica, Uva ursi. Tiodrix HR®: Thioctic Acid.

Abbreviations: M, male; F, female; CIOMS, Council for International Organizations of Medical Sciences auspices the workshop of international experts and is the same that RUCAM (Rousel Uclaf Causality Assessment Method which supported the event); WHO, World Health Organization; NA, not available; HILI, herbals-induced liver injury.

agent. One case (Case 15) used co-medications with four drugs (levothyroxine, omega 3, glucosamine and condroitin) for chronic diseases and one herbal medicine (*Copaifera langsdorfii Desf*). In Cases 13 and 14 other HDS were taken at the same temporal sequence with the culprit agent (30 ervas® tea and Nutritional Shake Mix [formula 1] and Personal Protein Power, respectively). In Case 12 the co-medications (30 ervas® tea and *E. giganteum*) were taken before the onset of liver injury.

We validated botanically species named in each study. Table 2 shows the evaluation of information available about botanical material in each study and botanical assessment including the Latin binomials using Medical Plants Names Services (MPNS).

Inadequate information for taxonomical assessment was found in 26% cases, most of them related with the use of Herbalife® products.

Liver biochemistry of the cases included in this analysis is shown in Table 2. The most frequent type of liver damage was hepatocellular in eight cases (35%), followed by cholestatic in five cases (22%) and mixed in two cases (9%). Three cases (13%) presented positive autoantibodies titers.

In relation to severity, 15 (65%) cases required hospitalization, five patients (22%) developed acute liver failure (ALF) and two died (Cases 10 and 11) (Table 2). Complete resolution was documented in 12 cases (52%) with a median recovery time of 60 days (4–540 days). Eleven of these cases (58%) resolved before 1 year. In contrast, five cases (22%) met definition for chronicity (Medina-Caliz et al., 2016). Case 9 resolved more than 500 days after HDS discontinuation.

Causality assessment tools were used for case ascertainment. The CIOMS (Council for International Organizations of Medical Sciences)/RUCAM (Roussel Uclaf Causality Assessment Method) scale (Danan & Benichou, 1993) was used to assess causality in 11 cases and yielded a score of highly probable for three patients (13%), probable for six patients (26%) and possible for two patients (9%). Of note, there was a positive re-challenge in four cases (Cases 2, 4, 5, and 17). The WHO scale (WHO-UMC system for standardized case causality assessment, 2019) was applied to one case yielding a score of probable. The Karch-Lasagna scale (Karch & Lasagna, 1977) was applied to Case 3, who was classified as a probable case (Table 1). The Teschke, Schwarzenboeck, and Hennermann's algorithm (Teschke, Schwarzenboeck, & Hennermann, 2008) was applied in Case 18 as possible causality. In the remaining cases (Cases 4, 5, 6, 8, 15, 19, 20, 21, and 22) no causality assessment tool was used, but the cases had enough information to ascertain causality.

The clinical characteristics of the current series of cases were compared to those of the Spanish DILI Registry (Medina-Caliz et al., 2018), US DILIN (Navarro et al., 2014), and a large series from China (Zhu et al., 2018) in Table 3. The proportion of hospitalization and mortality due to ALF was similar across the studies, with 65% and 9%, respectively, in the current study. However, the frequency of hepatocellular damage was lower (50%) and the frequency of rechallenge (22%) was higher in the LA cases than in the other registries. In addition, chronic cases (28%) accounted for a higher proportion in the LA cases than in the other studies.

TABLE 2 Biochemical parameters in 23 published cases of Herbal and Dietary Supplements induced liver injury in Latin American

Patient no.	Botanical or brand name	Latin binomials using Medical Plants Names Services (MPNS)	Total bilirubin (mg/dL)	ALT (UI/L)	ALP (UI/L)	Type liver injury, liver biopsy[a]	Hospitalization	Outcome
01	*Aloe Vera*	*Aloe vera* (L.) Burm.f. [Asphodelaceae]	13.0	935	200	Hepatocellular	Yes	Resolved
02	*Argemona mexicana* L.	*Argemone mexicana* L. [Papaveraceae]	2.5	211	434	Mixed	No	Resolved, 46 d
03	*Camellia sinensis*	*Camellia sinensis* (L.) Kuntze [Theaceae]	2.1	841	100	Mixed	Yes	Resolved, 4 d
04	*Centella asiatic*	*Centella asiatica* (L.) Urb. [Apiaceae]	4.2	1,193	503	Granulomatous acute hepatitis, marked cellular necrosis	No	Resolved, 60 d UDCA 10 mg/kg/day ASMA: 1/160 ANA: 1/320
05	*Centella asiatica*	*Centella asiatica* (L.) Urb. [Apiaceae]	19.9	1,694	472	Chronic hepatitis with cholestasis, granulomas and cirrhotic transformation	No	UDCA 10 mg/kg/d normalization liver parameter, 60 d. 5-y follow-up
06	*Centella asiatica*	*Centella asiatica* (L.) Urb. [Apiaceae]	3.9	324	484	Granulomatous acute hepatitis with necrosis	No	Resolved, 30 d UDCA 10 mg/kg/day
07	*Cochlospermum vitifolium*	*Cochlospermum vitifolium* (Willd.) Spreng. [Bixaceae]	7.9	221	1,201	Cholestasis Steatohepatitis with fibrosis	Yes	Resolved, 180 d ANA: 1:80
08	*Crotalaria juncea*	*Crotalaria juncea* L. [Fabaceae]	0.6	NA	122	Sinusoidal obstruction syndrome	Yes	Normal liver biopsy 575 d
09	Euforia®	*Euterpe oleracea* Mart. [Arecaceae], Garcinia × mangostana L. [Clusiaceae], Aloe vera (L.) Burm. f. [Asphodelaceae], *Nigella sativa* L. [Ranunculaceae], *Vaccinium angustifolium* Aiton [Ericaceae], *Punica granatum* L. [Lythraceae], *Camellia sinensis* (L.) Kuntze [Theaceae], *Morinda citrifolia* L. [Rubiaceae], *Lycium barbarum* L. [Solanaceae]	17.6	837	134	Submassive necrosis	Yes	Resolved, 540 d ANA: 1:320
10	Herbalife®	Data not available	15.0	443	144	Hepatocellular	Yes	ALF, death
11	Herbalife®	Data not available	0.4	78	169	Cholestasis	No	Resolved, 60 d
12	Herbalife®	Data not available	NA	NA	NA	Hepatoportal sclerosis	No	Chronic
13	Herbalife®	Data not available	NA	NA	NA	Hepatoportal sclerosis	No	Chronic
14	Herbalife®	Data not available	17.5	847	866	Cholestatic hepatitis	Yes	Resolved, 147 d

(Continues)

TABLE 2 (Continued)

Patient no.	Botanical or brand name	Latin binomials using Medical Plants Names Services (MPNS)	Total bilirubin (mg/dL)	ALT (UI/L)	ALP (UI/L)	Type liver injury, liver biopsy[a]	Hospitalization	Outcome
15	*Hypericum perforatum*	*Hypericum perforatum* L. [Hypericaceae] *Copaifera langsdorffii* Desf. [Fabaceae]	9.0	1,667	NA	Hepatocellular	No	Resolved, 49 d
16	Shen- Min®	*Reynoutria multiflora* (Thunb.) Moldenke [Polygonaceae], *Actaea racemosa* L. [Ranunculaceae], *Piper nigrum* L. [Piperaceae], *Actaea racemosa* L. [Ranunculaceae], *Ginkgo biloba* L. [Ginkgoaceae], Reynoutria multiflora (Thunb.) Moldenke [Polygonaceae], *Arctium lappa* L. [Asteraceae], *Capsicum annuum* L. [Solanaceae], *Glycine max* (L.) Merr. [Fabaceae], *Aesculus hippocastanum* L. [Sapindaceae], *Cinnamomum verum* J.Presl [Lauraceae], *Arctostaphylos uva-ursi* (L.) Spreng. [Ericaceae]	12.3	2,922	153	Hepatocellular	Yes	Resolved, 25 d
17	Tiodrix HR®	Dietary supplement. It is not appropriate to indicate classification.	1.5	113	1,237	Cholestasis Parenchymal bilirubin stasis with isolated necrotic hepatocyte	Yes	Resolved, 113 d Macopapular rash in chest, arms and tights
18	*Ruellia bahiensis*	Cissus alata Jacq. [Vitaceae]	21.8	1,290	NA	Multilobular necrosis	Yes	ALF, orthotopic liver transplant
19	*Camellia sinensis*	*Camellia sinensis* (L.) Kuntze [Theaceae]	2.52	1,500	482		Yes	Resolved, 60 d
20	*Carthamus tinctorius*	*Carthamus tinctorius* L. [Asteraceae]	NA	NA	NA	Necrosis	Yes	ALF, transplant
21	*Carthamus tinctorius*	*Carthamus tinctorius* L. [Asteraceae]	NA	NA	NA	Necrosis	Yes	ALF, transplant, death
22	*Carthamus tinctorius*	*Carthamus tinctorius* L. [Asteraceae]	NA	NA	NA	Necrosis	Yes	ALF, transplant
23	*Piper methysticum*	*Piper methysticum* G. Forst. [Piperaceae]	12.40	NA	NA	Submassive necrosis	Yes	ALF, transplant

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibody; AMA, anti-mitochondrial antibodies; ALF, acute liver failure; UDCA, ursodeoxycholic acid; d, day; NA, not available.

Note: Case no. 10 is included in the Latin America DILI Network database. Sinusoidal Obstruction Syndrome also known as Hepatic Veno-Occlusive Disease.

[a]Liver biopsy findings are shown when available.

TABLE 3 Clinical characteristics of herbal and dietary supplements-induced liver injury cases across the main study cohorts

	Prospective		Retrospective	
	Spanish DILI Registry (Medina-Caliz et al., 2018)	US DILIN (Navarro et al., 2014)	China (Zhu et al., 2018)	Our study
N	32	85	488	23
Age (mean)	48	47[a]	45	44
Female (%)	63	65	72	87
Hospitalization (%)	63	68	100	65
Hepatocellular damage (%)	94	71	86	35
Liver transplant, *n* (%)	1 (3.1)	11 (13)	1 (0.2)	5 (22)
Death due to ALF, *n* (%)	1 (3.1)	3 (4)	19 (4)	2 (9)
Rechallenge (%)	9	ND	7	17
Chronicity, *n* (%)	0	ND	14[b]	22
Main herbs	Herbalife® products, *Camellia sinensis*		Herbal decoction with unknown constituents	Herbalife® products, *Centella asiatica* *Carthamus tinctorius*

[a]Median; ND, no data.
[b]Including patients with sustained liver-related laboratory, radiologic, or histologic abnormalities at 6 months after HILI onset.

4 | DISCUSSION

Data derived from different DILI registries shows that the contribution of HDS to the total number of cases of hepatotoxicity varies across countries, ranging from 1.3% to 62% (Andrade et al., 2018). Asian countries, due to the use of Chinese traditional medicine and related compounds, exhibited higher figures (Shen et al., 2019; Suk et al., 2012; Wai et al., 2007; Zhu et al., 2018). However, there is also an upward trend in Western countries, as demonstrated in reports from the United States (Navarro et al., 2014) and Spain (Medina-Caliz et al., 2018). Because the use of herbal remedies is common in LA, information on the frequency and characteristics of the adverse effects related to HDS and the mechanisms involved have particular relevance.

In this systematic review we sought to review demographic, clinical characteristics and biochemical parameters of HDS hepatotoxicity in LA retrieving published case reports and case series. Moreover, this analysis complements a previous study that described the features of idiosyncratic DILI in several countries in LA, in which HILI was not considered (Hernández et al., 2014).

LA has a large herbal market that is an important part of its traditional medicine (Bessone et al., 2016). Some herb species identified in this analysis such as *Argemone mexicana* L. and *Cochlospermum vitifolium* were endemic from LA. Besides, *Aloe vera*, *Camellia sinensis* and *C. asiatica* species, are included in the composition of phototherapies and manufactured food supplements used in several LA countries, despite being well known hepatotoxins (Navarro & Lucena, 2014).

The most frequent single herbal ingredients involved in HDS hepatotoxicity in the current cases series was *C. asiatica*, in 20% of cases. Conversely, *C. sinensis* was the most frequent single herbal ingredient involved in HDS hepatotoxicity in Spanish DILI Registry (Medina-Caliz et al., 2018), whereas only one HILI case due to *C. sinensis* was identified among the cases analyzed in the present study.

Herbalife®, various multi-ingredient products, was the most reported causative compound group in the current series. This finding is consistent with those reported by Björnsson et al. (2013) in a population-based study in Iceland. The composition of these products is not well disclosed and may vary over the years. In the current analyses the reported Herbalife® cases spanned from 2007 to 2013.

Other cases related to acute hepatitis associated with conjugated linoleic acid, the main component of *C. tinctorius* oil, used as a weight loss supplement, have been reported in Europe (Nortadas & Barata, 2012; Ramos, Mascarenhas, Duarte, Vicente, & Casteleiro, 2009). In an experimental study (Schuster et al., 2018), a diet containing linoleic acid and its oxidized linoleic acid metabolite caused hepatic injury in mice. Euforia®, Shen-Min®, and Tiodrix HR® herbal supplements have in their composition multiple ingredients (see Table 2) that have been related to severe acute liver damage (Abdel-Zaher, Abdel-Hady, Mahmoud, & Farrag, 2008; But, Tomlinson, & Lee, 1996; Gavric, Ribnikar, Smid, Luzar, & Stabuc, 2018; Guzman et al., 2009; Mazzanti et al., 2004; Navarro et al., 2017; Park, Mann, & Ngu, 2001; Stadlbauer et al., 2005; Yu et al., 2011, 2017). However, to ascertain the ingredient responsible in multi-ingredient HDS is often unfeasible. In such cases CIOMS/RUCAM scale cannot discriminate between the agents and the case has to be finally ascribed to the combination of products (García-Cortés, Stephens, Lucena, Fernández-Castañer, & Andrade, 2011). In the remaining cases, concomitant drugs did not have a plausible temporal relationship with the hepatic adverse reaction, as they were taken on a chronic basis or were stopped long before the reaction appeared and/or the compound has not been previously related with hepatotoxicity.

As reported by other studies in the United States and Europe (Navarro et al., 2014) the main reason for HDS use in the current cohort was weight loss, in more than half of the cases. Rates of obesity have increased in some LA countries such as Cuba, Mexico, and Brazil since the 1990s (Ng et al., 2014). Noticeably, the majority of the HDS cases included in the current series were young females. This fact may be related to the greater consumption of supplements by women, especially for weight loss (Bailey, Gahche, Miller, Thomas, & Dwyer, 2013), similarly to what has been reported by the Spanish DILI Registry (García-Cortés et al., 2008; Medina-Caliz et al., 2018), the DILIN group (Navarro et al., 2014) and in Chinese studies (Zhu et al., 2018).

Although the hepatocellular pattern of liver damage predominated (35%), the proportion was lower to that reported in other studies (Navarro et al., 2014; Zhu et al., 2018). According to the Spanish DILI Registry 94% of the HDS lesions were hepatocellular (García-Cortés et al., 2008; Medina-Caliz et al., 2018). Evidence of autoimmunity was also found in three cases in the current series. Some studies have suggested that hepatic injury due HDS can adopt clinical characteristics of autoimmune-like hepatitis (AIH), such as the appearance of autoantibodies and hepatic infiltration of immune competent cells (Sebode, Schulz, & Lohse, 2017). Up to date, it is not clear whether HDS may unmask or induce AIH causing HILI with autoimmune features (Cavalcante, Pinheiro, Fonseca, & Machado, 2018).

In the current case series 65% of the patients required hospitalization. Previous report from the US DILIN group and the Spanish DILI Registry showed that HILI patients required more medical interventions and had a higher risk of a severe outcome compared to DILI (García-Cortés et al., 2008; Navarro et al., 2014).

Complete resolution of the clinical picture was evident in 12 (52%) cases, five cases (22%) developed ALF and underwent liver transplantation, and one of them died after transplantation (Case 21). Only one case (4%) in the current HILI series, which was related to the use of a Herbalife® product, developed ALF and died. A U.S. study revealed that herbal products were responsible for a high percentage of referrals for liver transplantations (Hillman et al., 2016). Moreover, our results are in concordance with those from Israel and Switzerland showing that 9% of cases related to Herbalife® products presented with fulminant liver failure (Elinav et al., 2007; Schoepfer et al., 2007). Several cases of liver damage from this product were also reported to the Spanish national pharmacovigilance system (Manso, Lopez-Rivas, Duque, & Salgueiro, 2008).

Our findings showed a variability of histological lesions. These results are in agreement with the histological entities described in the DILIN study, where four patterns—acute hepatitis, chronic hepatitis or chronic cholestasis, and cholestatic hepatitis—were the more predominant histological entities found (Kleiner et al., 2014). Moreover, a similar histological profile including chronic hepatitis with inflammatory findings and fibrosis associated with chronic hepatitis where observed in other studies (Devarbhavi et al., 2010).

Indeed, in this systematic review, five cases (22%) were chronic, four of them at the time of diagnosis (Cases 5, 8, 13, and 14). One of these chronic cases was due to the consumption of *C. asiatica*, which caused chronic hepatitis with cholestasis, granulomas and cirrhotic transformation. These clinical manifestations occurred upon prolonged consumption of the herb. Treatment discontinuation and liver tests monitoring showed normalization of liver parameter after 5 years of follow-up. Another chronic case presenting with sinusoidal obstruction syndrome was related to *Croatalaria juncea*. This disorder is known to be caused by ingestion of certain species of plants that contain pyrrolizidine alkaloids and hepatic histopathology consists of liver degeneration, necrosis and cirrhosis (Lyford et al., 1976; Zhuge et al., 2019). In the HILI case herein described, a liver biopsy was normal after 575 days. Two additional cases related to Herbalife® presented with a chronic histologic lesion—hepatoportal sclerosis or the now recognized term "porto-sinusoidal vascular disease" (De Gottardi et al., 2019)—making the frequency of chronic cases in this series higher than that observed in other cohorts.

In the current series unintentional re-challenge was noticeable. HDS products are generally promoted as being "natural", and therefore perceived as innocuous by consumers and many health-care professionals. Due to lack of rigorous regulation, the need for the manufacturer of the nutraceutical to prove efficacy, safety and quality of a marketed product is less strongly enforced than in the pharmaceutical sector. Therefore, many available products might be ineffective but measures to ensure safety become a crucial policy (Williamson, Liu, & Izzo, 2019). Indeed, according to Verma & Thuluvath (2007), 31–40% of patients do not disclose HDS use. Thus, patients tend to underreport HDS use to their physicians and re-exposure to the product is not unusual. In addition, the information on the botanical names provided in published HILI cases is not homogeneous hindering the identification of the culprit product. We therefore suggest that authors may use the botanical name recorded in the Medical Plants Names Services as a way of standardizing HDS nomenclature.

The CIOMS/RUCAM scale was the tool more frequently used for causality assessment despite its known limitation, particularly in the setting of multi-ingredient products, that makes the identification of a single causative agent very difficult (Andrade et al., 2018). Additional limitations when applying the CIOMS/RUCAM scale are the lack of previous information about adverse events induced by herbal products or incomplete timing criteria (García-Cortés et al., 2011). An interesting fact is that three cases in the current series had a CIOMS/RUCAM score above eight (highly probable). However, it should be noted that these cases had a positive re-challenge, which may have contributed to the higher probability scores.

Despite a thorough search strategy with no language restriction and including specific LA databases, the limited number of reports may be the most remarkable finding and underscores the need for high quality data reporting of cases of liver injury in LA. Also, the criteria for DILI definition and diagnostic approach of the cases was varied probably due to the long period of search spanning across 40 years, pointing out the need for consistent publication practice when such injuries are reported. Nevertheless, our systematic review provides the best available evidence on the topic. Indeed, our results paralleled those found in other studies conducted in United States

(Navarro et al., 2014), Europe (Medina-Caliz et al., 2018) and China (Zhu et al., 2018). The higher frequency of chronic HILI and cases with a worst outcome may be reflecting some sort of publication bias, as rare and severe reports are more prone to publication, suggesting an underreporting of less serious cases.

In addition, unlabeled ingredients, added intentionally, accidentally, or as a by-product of the manufacturing process, is another aspect in the improvement of the detection and management of HILI. In the US, studies of selected HDS products have demonstrated discrepancies between product labels and chemical analysis in 51% of potentially hepatotoxic HDS products tested (Navarro et al., 2019). Other studies have searched for potential hepatotoxins among HDS implicated in causing liver injury and identified the active ingredients to attenuate toxicity as far as possible in these products (Zhang et al., 2019). Further studies of HDS associated with hepatotoxicity are needed to better define the mechanisms and ingredients responsible for the observed liver injury. Herein, we highlight the relevance of conducting phytopharmacological research following the recommendations of a recent consensus best practice document (Heinrich et al., 2020).

In conclusion, this systematic review provides relevant information about clinical features associated with HDS hepatotoxicity and identifies the most common culprit agents in LA. Our analysis confirms the signature of HDS-induced liver injury predominantly affecting young females with hepatocellular type of damage, a higher rate of acute liver failure and inadvertent re-challenge, but distinctly finding a higher rate of chronicity than previously reported. This study also underscores the challenge of causality assessment in patients with hepatotoxicity suspicion taking multi-ingredient HDS because of the frequent mislabelling or unlisted ingredients and unknown concentrations. Our systematic review also highlights the need for consistent publication practice when HDS hepatotoxicity is reported. Thus, reporting hepatic adverse reactions would be essential to foster HDS liver safety particularly in this region of the world.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Guarantor of the study Maria Isabel Lucena. Genario Santos, Jessica Gasca collected and analyzed data and wrote manuscript and contributed equally to this work; Inmaculada Medina-Caliz, Vinicius Nunes, Maria Schinnoni, Maria Rosario Cabello analyzed data. Maria Isabel Lucena, Raul J. Andrade, Raymundo Parana designed the study, participated in the writing and made the overview of the manuscript.

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