

1  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

# Profile of Herbal and Dietary Supplements Induced Liver Injury in Latin America: A systematic review of published reports

**Short title:** A systematic review of HDS hepatotoxicity in Latin America

**Genario Santos**<sup>1§</sup>, **Jessica Gasca**<sup>2§</sup>, **Raymundo Parana**<sup>1</sup>, **Vinicius Nunes**<sup>1</sup>, **Maria Schinnoni**<sup>1</sup>, **Inmaculada Medina-Caliz**<sup>3</sup>, **M Rosario Cabello**<sup>1a</sup>, **M Isabel Lucena**<sup>1,2, a\*</sup>, **Raul J Andrade**<sup>3a</sup>

§ These authors contributed equally to this work.

<sup>1</sup>Núcleo de Hepatologia, Hospital Universitário Prof. Edgard Santos-UFBA, Salvador, Brazil

<sup>2</sup>UICEC IBIMA, Plataforma SCReN (Spanish Clinical Research Network), Servicio de Farmacología Clínica, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Spain

<sup>3</sup>Servicio de Aparato Digestivo, Instituto de Investigación Biomédica de Málaga – IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Malaga, Spain

<sup>a</sup>CIBERehd, Madrid, Spain.

**\* Correspondence:**

M<sup>a</sup> Isabel Lucena, M.D., PhD

Departamento de Farmacología

Facultad de Medicina,  
Universidad de Málaga,  
Boulevard Louis Pasteur, 32  
29071 Málaga, Spain.  
Tel: (+34) 952 131572; Fax: (+34) 952 131568;  
E-mail: lucena@uma.es

### **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 MIL

GS, JG collected and analysed data and wrote manuscript and contributed equally to this work; I M-C, VN, MS, MRC analysed data. MIL, RJA, RP designed the study, participated in the writing and made the overview of the manuscript.

### **Funding**

The present study has been supported by grants of the Instituto de Salud Carlos III cofounded by Fondo Europeo de Desarrollo Regional – FEDER (contract numbers: PT13/0002/0020 and PT17/0017/0020; PI-0310-2018, PI-0285-2016, PI-0274-2016, PI18-00901, PI18/01804).

CIBERehd is funded by Instituto de Salud Carlos III. SCReN and CIBERehd are funded by Instituto de Salud Carlos III.

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

### **Acknowledgments**

We gratefully acknowledge the Maria Emilia Pedreira Freire de Carvalho Foundation, Salvador-Bahia, for financial and logistical support to the Scientific Mission of the predoctoral student Genario Santos at the University of Malaga.

**Disclosure:** None

**Keywords:** herbal and dietary supplements -induced liver injury, Latin America, hepatotoxicity, phenotypic presentations, outcome.

### **Article types**

Systematic Review

© 2021. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <https://creativecommons.org/licenses/by-nc-nd/4.0/>(opens in new tab/window)

### **Abstract**

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

i1 to describe the clinical features of HDS related hepatotoxicity in this region. We search  
i2  
i3  
54 in PubMed, Web of Science, Scopus and specific LA databases according to PRISMA  
i5  
i6 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 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.

## **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 et al., 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

i7 and the Brazilian market turnaround is estimated to be US \$400 million, representing 12%  
i8  
i9 increase per year, which is higher than that of conventional drugs that are expected to



6 recorded species (Valdivia-Correa et al., 2016) just behind China that ranks first in the world with more than 5000 species (Liu et al., 2016).

0  
1 In general, the real incidence of HDS-induced liver injury (HILI) remains unknown.  
2 Recent efforts across the world in population-based studies or prospectively collecting  
3 cases of hepatotoxicity have started to provide some figures on the incidence and relative  
4 prevalence of HDS induced liver injury compared to conventional drugs. According to  
5 the US Drug-Induced Liver Injury Network (DILIN), the annual incidence of drug- and  
6 herbal and dietary supplement hepatotoxicity is estimated at 2.7 cases per 100,000 adults  
7 in 2014 with 43% of the incident cases being attributed to HDS (Vega et al., 2017), an  
8 extrapolated HDS incidence of 3 cases per 100.000 inhabitants in Iceland (Björnsson et  
9 al., 2013), while Suk et al reported figures of DILI and HILI hospitalized cases of 12 /  
10 100,000 habitants per year between 2004-2007 in South Korea (Suk et al., 2012). A recent  
11 three-year retrospective multicentre study from Mainland China reported an average  
12 incidence of DILI and HILI in the general population of 23.80 per 100,000 persons (Shen  
13 et al., 2019). A study published by the Spanish DILI group, showed that 6% of the  
14 hepatotoxicity cases were related to HDS, while in the US DILIN the figures reached  
15 14% during 2013-2014 (Medina-Caliz et al., 2018; Navarro et al., 2014). In the LATIN  
16 DILI Network, it is estimated that HDS hepatotoxicity represents 10% of the causes of  
acute liver injury (Bessone et al., 2016) although the characteristics of HDS  
hepatotoxicity in LA have not yet been published in detail (Byeon et al., 2019).

0  
1 Up to date the reports of HDS hepatotoxicity published in scientific journals are the only  
2 epidemiological information available in LA. Hence, we aimed to systematically review  
3 published case reports and case series of HDS-induced liver injury in LA in order to  
4  
5  
6

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.

## **Material and methods**

### **a) 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.

### **b) Eligibility criteria**

The criteria for DILI definition according to Bénichou (Bénichou, 1990) and Aithal et al. (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

i6  
i7  
i8

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





case (case 15) used co-medications with four drugs (levothyroxine, omega 3, glucosamine

and chondroitin) for chronic diseases and one herbal medicine (*Copaifera langsdorffii* 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 8 cases (35%), followed by cholestatic in 5 cases (22%) and mixed in 2 cases (9%). Three cases (13%) presented positive autoantibodies titres.

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 one 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 and 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.) was applied to one case yielding a score of probable. The Karch-Lasagna scale (Karch and Lasagna, 1977) was applied to case 3, who was classified as a probable case (Table 1). The Teschke, Schwarzenboeck and Hennermann's algorithm (Teschke et al., 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 re-challenge (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.

## 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 USA (Navarro et al., 2014) and Spain



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 *Carthamus tinctorius* oil, used as a weight loss supplement, have been reported in Europe (Nortadas and Barata, 2012; Ramos et al., 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 et al., 2008; But et al., 1996; Gavric et al., 2018; Guzman et al., 2009; Mazzanti et al., 2004; Navarro et al., 2017; Park et al., 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 et al., 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 USA 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 et al., 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 et al., 2017). Up to date, it is not clear whether HDS may unmask or induce AIH causing HILI with autoimmune features (Cavalcante et al., 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 US 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 et al., 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 were 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 *Centella 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 five 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 - hepatportal 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





underscores the need for high quality data reporting of cases of liver injury in LA. Also,



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.

## References

- Abdel-Zaher, A. O., Abdel-Hady, R. H., Mahmoud, M. M., and Farrag, M. M. Y. (2008). The potential protective role of alpha-lipoic acid against acetaminophen-induced hepatic and renal damage. *Toxicology* 243, 261–270. doi:10.1016/j.tox.2007.10.010.
- Agollo Costa, M., Jankiel Miszputen, S., and Diament, J. (2014). Hypericum perforatum -induced hepatotoxicity with possible association with copaiba (Copaifera langsdorffii Desf): case report. *Einstein (Sao Paulo)* 12, 355–357. doi:10.1590/S1679-45082014RC2953.
- Aithal, G. P., Watkins, P. B., Andrade, R. J., Larrey, D., Molokhia, M., Takikawa, H., et al. (2011). Case Definition and Phenotype Standardization in Drug-Induced Liver Injury. *Clin. Pharmacol. Ther.*, 1–10. doi:10.1038/clpt.2011.58.
- Andrade, R. J., Medina-Caliz, I., Gonzalez-Jimenez, A., Garcia-Cortes, M., and Lucena, M. I. (2018). Hepatic Damage by Natural Remedies. *Semin. Liver Dis.* 38, 21–40. doi:10.1055/s-0038-1623518.

Bailey, R. L., Gahche, J. J., Miller, P. E., Thomas, P. R., and Dwyer, J. T. (2013). Why

US adults use dietary supplements. *JAMA Intern. Med.* 173, 355–361.

doi:10.1001/jamainternmed.2013.2299.

Becker, M. W., Lourençone, E. M. S., Mello, A. F. De, Branco, A., Filho, E. M. R.,

Blatt, C. R., et al. (2019). Liver transplantation and the use of KAVA: Case report.

*Phytomedicine* 56, 21–26. doi:https://doi.org/10.1016/j.phymed.2018.08.011.

Bénichou, C. (1990). Criteria of drug-induced liver disorders: Report of an International

Consensus Meeting. *J. Hepatol.* 11, 272–276. doi:10.1016/0168-8278(90)90124-A.

Bessone, F., Hernandez, N., Lucena, M. I., and Andrade, R. J. (2016). The latin

American dili registry experience: A successful ongoing collaborative strategic

initiative. *Int. J. Mol. Sci.* 17, 1–12. doi:10.3390/ijms17030313.

Björnsson, E. S., Bergmann, O. M., Björnsson, H. K., and Kvaran, R. B. (2013).

Incidence , Presentation , and Outcomes in Patients With Drug-Induced Liver

Injury in the General Population of Iceland. *Gastroenterology* 144, 1419-1425.e3.

doi:10.1053/j.gastro.2013.02.006.

But, P. P., Tomlinson, B., and Lee, K. L. (1996). Hepatitis related to the Chinese

medicine Shou-wu-pian manufactured from *Polygonum multiflorum*. *Vet. Hum.*

*Toxicol.* 38, 280–282.

Byeon, J. H., Kil, J. H., Ahn, Y. C., and Son, C. G. (2019). Systematic review of

published data on herb induced liver injury. *J. Ethnopharmacol.* 233, 190–196.

doi:10.1016/j.jep.2019.01.006.

Cárdenas, A., Restrepo, J. C., Sierra, F., and Correa, G. (2006). Acute Hepatitis Due to

Shen-Min A Herbal Product Derived From *Polygonum multiflorum*. *J Clin*



Danan, G., and Benichou, C. (1993). Causality assessment of adverse reactions to

8  
59  
0

6  
drugs--I. A novel method based on the conclusions of international consensus  
meetings: application to drug-induced liver injuries. *J. Clin. Epidemiol.* 46, 1323–  
1330.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
de Ataíde, E. C., Perales, S. R., de Oliveira Peres, M. A., da Costa, L. B. E., Quarella,  
F., Valerini, F. G., et al. (2018). Acute Liver Failure Induced by *Carthamus*  
tinctorius Oil: Case Reports and Literature Review. *Transplant. Proc.* 50, 476–477.  
doi:<https://doi.org/10.1016/j.transproceed.2018.01.010>.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
De Gottardi, A., Rautou, P., Schouten, J., Rubbia-brandt, L., Leebeek, F., Trebicka, J.,  
et al. (2019). Porto-sinusoidal vascular disease : proposal and description of a  
novel entity. *Lancet Gastroenterol. Hepatol.* 4, 399–411. doi:10.1016/S2468-  
1253(19)30047-0.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
Devarbhavi, H., Dierkhising, R., Kremers, W. K., Sandeep, M. S., Karanth, D., and  
Adarsh, C. K. (2010). Single-center experience with drug-induced liver injury from  
India: causes, outcome, prognosis, and predictors of mortality. *Am. J.*  
*Gastroenterol.* 105, 2396–2404. doi:10.1038/ajg.2010.287.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
Ferreira Rios, F., Antônio, L., Freitas, R. De, Codes, L., Oliveira Santos Junior, G.,  
Schinoni, M. I., et al. (2016). Hepatoportal sclerosis related to the use of herbal and  
nutritional supplements. Causality or coincidence ? *Ann. Hepatol.* 15, 932–938.  
doi:10.5604/16652681.1222113.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
Garcia-Alvarez, A., Egan, B., de Klein, S., Dima, L., Maggi, F. M., Isoniemi, M., et al.  
(2014). Usage of Plant Food Supplements across Six European Countries: Findings  
from the PlantLIBRA Consumer Survey. *PLoS One* 9, e92265. Available at:  
<https://doi.org/10.1371/journal.pone.0092265>.







- 6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59
- Liu, C., Fan, H., Li, Y., and Xiao, X. (2016). Research Advances on Hepatotoxicity of Herbal Medicines in China. *Biomed Res. Int.* 2016, 14. doi:10.1155/2016/7150391.
- Lyford, C. L., Vergara, G. G., and Moeller, D. D. (1976). Hepatic veno-occlusive disease originating in Ecuador. *Gastroenterology* 70, 105–108. doi:10.1016/S0016-5085(76)80410-6.
- Manso, G., Lopez-Rivas, L., Duque, J. M., and Salgueiro, E. (2008). Spanish reports of hepatotoxicity associated with Herbalife products. *J. Hepatol.* 49, 281–289. doi:10.1016/j.jhep.2008.05.007.
- Martínez-Rodríguez, L., Murguía-Hernández, K., García-Juárez, I., Uribe-Esquivel, M., and Gómez-Reyesa, E. (2015). La historia oscura de la rosa amarilla: un reporte de caso de toxicidad hepática asociado al consumo de *Cochlospermum vitifolium* como remedio herbolario. The dark story of the yellow rose: A case report of hepatotoxicity associated with *Cochlospermum viti*. *Rev. Gastroenterol. México* 80, 220–222. doi:10.1016/j.rgm.2015.02.003.
- Mazzanti, G., Battinelli, L., Daniele, C., Mastroianni, C. M., Lichtner, M., Coletta, S., et al. (2004). New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from *Polygonum multiflorum*. *Ann. Intern. Med.* 140, W30. doi:10.7326/0003-4819-140-7-200404060-00042-w3.
- Medina-Caliz, I., Garcia-Cortes, M., Gonzalez-Jimenez, A., Cabello, M. R., Robles-Diaz, M., Sanabria-Cabrera, J., et al. (2018). Herbal and Dietary Supplement-Induced Liver Injuries in the Spanish DILI Registry. *Clin. Gastroenterol. Hepatol.* 16, 1495–1502. doi:10.1016/j.cgh.2017.12.051.



6  
Garcia-Cortes, M., et al. (2016). Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. *J. Hepatol.* 65, 532–542. doi:10.1016/j.jhep.2016.05.003.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
Meléndez González, C. A. (2013). Riesgos de la herbolaria : reporte de un caso de hepatitis por cardo santo ( *Argemone mexicana* L ) Risks of herbalism : a case report of Mexican poppy ( *Argemone mexicana* L ) induced liver toxicity. *Medwave* 13, :e5763. doi:10.5867/medwave.2013.07.5763.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Mensual-Moreno, E., Lizarábal-García, M., Ruiz-Soler, M., Silva-Suarez, N., Andrade-Bellido, R., Lucena-González, M., et al. (2015). Reporte de casos de lesión hepática inducida por medicamentos en un centro hospitalario de referencia del estado Zulia, Venezuela. *Invest. Clin.* 56, 3–12.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Morris, C. A., and Avorn, J. (2003). Internet Marketing of Herbal Products. *J. Am. Med. Assoc.* 290, 1505–1509. doi:10.1001/jama.290.11.1505.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Muñoz, P. A., Angulo, N., Agudelo-Agudelo, J., and Gaviria, G. (2009). Hepatitis asociada a infusiones acuosas de té verde : a propósito de un caso. Hepatitis associated with aqueous green tea infusions: a case study. *Soc. Española Farm. Hosp.* 30, 289–291. doi:10.1016/S1130-6343(09)72471-7.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Navarro, V., Avula, B., Khan, I., Verma, M., Seeff, L., Serrano, J., et al. (2019). The Contents of Herbal and Dietary Supplements Implicated in Liver Injury in the United States Are Frequently Mislabeled. *Hepatol. Commun.* 3, 792–794. doi:10.1002/hep4.1346.

0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
Navarro, V. J., Barnhart, H., Bonkovsky, H. L., Davern, T., Fontana, R. J., Grant, L., et al. (2014). Liver injury from herbals and dietary supplements in the U.S. Drug-

Induced Liver Injury Network. *Hepatology* 60, 1399–1408.

doi:10.1002/hep.27317.

Navarro, V. J., and Lucena, M. I. (2014). Hepatotoxicity induced by herbal and dietary supplements. *Semin. Liver Dis.* 34, 172–193. doi:10.1055/s-0034-1375958.

Navarro, V., Khan, I., Björnsson, E., Seeff, L. B., Serrano, J., and Hoofnagle, J. H.

(2017). Liver Injury from Herbal and Dietary Supplements HHS Public Access.

*Hepatology* 65, 363–373. doi:10.1002/hep.28813.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., et al.

(2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)* 384, 766–781.

doi:10.1016/S0140-6736(14)60460-8.

Nortadas, R., and Barata, J. (2012). Fulminant hepatitis during self-medication with conjugated linoleic acid. *Ann. Hepatol.* 11, 265–267.

doi:https://doi.org/10.1016/S1665-2681(19)31034-8.

Park, G. J., Mann, S. P., and Ngu, M. C. (2001). Acute hepatitis induced by Shou-Wu-

Pian, a herbal product derived from *Polygonum multiflorum*. *J. Gastroenterol.*

*Hepatol.* 16, 115–117.

Ramirez Rodriguez, N., Pabón Uego, C., Ortiz, E., Duchén, L., and Ávila, A. (2004).

Intoxicación por hierbas y su posible relación con encefalopatía hepática :

síndrome de Reye. *Rev. bol. ped.* 43, 86-88. Disponible en:

<http://www.scielo.org.bo/sci>.

Ramos, R., Mascarenhas, J., Duarte, P., Vicente, C., and Casteleiro, C. (2009).

Conjugated Linoleic Acid-Induced Toxic Hepatitis: First Case Report. *Dig. Dis. Sci.* 54, 1141–1143. doi:10.1007/s10620-008-0461-1.

Restrepo, J. C., Muñoz, J. F., Correa, G., Zuleta Tobón, J. J., Londoño, M., Botero, A., et al. (2008). Hepatotoxicidad detectada en un hospital de cuarto nivel en la ciudad de Medellín. *Acta Médica Colomb.* 33, 261–267.

Ridruejo, E., Castiglioni, T., and Silva, M. O. (2011). Thioctic Acid – Induced Acute Cholestatic Hepatitis. *Ann. Pharmacother.* 45, e43. doi:10.1345/aph.1Q035.

Santos Júnior, G. O., Ferreira, F., Raymundo, P., Foulon, L., Codes, M. de, and Noblat, L. de A. C. B. (2018). Fulminant hepatic failure caused by herbal supplies. *Brazilian J. Pharm. Sci.* 54, e17418. doi:https://dx.doi.org/10.1590/s2175-97902018000317418.

Schuster, S., Johnson, C. D., Hennebelle, M., Holtmann, T., Taha, A. Y., Kirpich, I. A., et al. (2018). Oxidized linoleic acid metabolites induce liver mitochondrial dysfunction, apoptosis, and NLRP3 activation in mice. *J. Lipid Res.* 59, 1597–1609. doi:10.1194/jlr.M083741.

Sebode, M., Schulz, L., and Lohse, A. W. (2017). “ Autoimmune ( -Like )” Drug and Herb Induced Liver Injury : New Insights into Molecular Pathogenesis. *Int. J. Mol. Sci. Rev.* 18. doi:10.3390/ijms18091954.

Seeff, L. B., Bonkovsky, H. L., Navarro, V. J., and Wang, G. (2015). Herbal Products and the Liver: A Review of Adverse Effects and Mechanisms. *Gastroenterology* 148, 517-532.e3. doi:10.1053/j.gastro.2014.12.004.

- Shen, T., Liu, Y., Shang, J., Xie, Q., Li, J., Yan, M., et al. (2019). Incidence and Etiology of Drug-Induced Liver Injury in Mainland. *Gastroenterology* 156, 2230-2241.e11. doi:10.1053/j.gastro.2019.02.002.
- Stadlbauer, V., Fickert, P., Lackner, C., Schmerlaib, J., Krisper, P., Trauner, M., et al. (2005). Hepatotoxicity of NONI juice: report of two cases. *World J. Gastroenterol.* 11, 4758–4760. doi:10.3748/wjg.v11.i30.4758.
- Stedman, C. (2002). Herbal Hepatotoxicity. *Semin Liver Dis* 22, 195–206. doi:10.1055/s-2002-30104.
- Suk, K. T., Kim, D. J., Kim, C. H., Park, S. H., Yoon, J. H., Kim, Y. S., et al. (2012). A Prospective Nationwide Study of Drug-Induced Liver Injury in Korea. *Am. J. Gastroenterol.* 107. Available at: [https://journals.lww.com/ajg/Fulltext/2012/09000/A\\_Prospective\\_Nationwide\\_Study\\_of\\_Drug\\_Induced.20.aspx](https://journals.lww.com/ajg/Fulltext/2012/09000/A_Prospective_Nationwide_Study_of_Drug_Induced.20.aspx).
- Tabajara de Oliveira Martins, D., Rodrigues, E., Casu, L., Benítez, G., and Leonti, M. (2019). The historical development of pharmacopoeias and the inclusion of exotic herbal drugs with a focus on Europe and Brazil. *J. Ethnopharmacol.* 240, 111891. doi:<https://doi.org/10.1016/j.jep.2019.111891>.
- Teschke, R., Schwarzenboeck, A., and Hennermann, K.-H. (2008). Causality assessment in hepatotoxicity by drugs and dietary supplements. *Br. J. Clin. Pharmacol.* 66, 758–766. doi:10.1111/j.1365-2125.2008.03264.x.
- Valdivia-Correa, B., Gómez-Gutiérrez, C., Uribe, M., and Méndez-Sánchez, N. (2016). Herbal medicine in Mexico: A cause of hepatotoxicity. A critical review. *Int. J. Mol. Sci.* 17. doi:10.3390/ijms17020235.

0 Vega, M., Verma, M., Beswick, D., Bey, S., Hossack, J., Merriman, N., et al. (2017).

6 The Incidence of Drug- and Herbal and Dietary Supplement-Induced Liver Injury:  
Preliminary Findings from Gastroenterologist-Based Surveillance in the Population  
of the State of Delaware. *Drug Saf.* 40, 783–787. doi:10.1007/s40264-017-0547-9.

1 Verma, S., and Thuluvath, P. J. (2007). Complementary and alternative medicine in

2 hepatology: review of the evidence of efficacy. *Clin. Gastroenterol. Hepatol.* 5,  
3 408–416. doi:10.1016/j.cgh.2006.10.014.

4 Wai, C.-T., Tan, B.-H., Chan, C.-L., Sutedja, D. S., Lee, Y.-M., Khor, C., et al. (2007).

5 Drug-induced liver injury at an Asian center: a prospective study. *Liver Int.* 27,  
6 465–474. doi:10.1111/j.1478-3231.2007.01461.x.

7 WHO-UMC system for standardized case causality assessment. World Health

8 Organization (WHO) — Uppsala Monitoring Centre. *Available from*

9 *http://www.who-umc.org/Graphics/24734.pdf*. Last accessed 2019 July 31.

10 Williamson, E. M., Liu, X., and Izzo, A. A. (2019). Trends in use, pharmacology, and

11 clinical applications of emerging herbal nutraceuticals. *Br. J. Pharmacol.* 177,

12 1227–1240. doi:10.1111/bph.14943.

13 World Health Organization. WHO Traditional Medicine Strategy: 2014–2023. World

14 Health Organization. WHO Traditional Medicine Strategy: 2014–2023. *Available*

15 *http://www.who.int/medicines/publications/Tradit*. Accessed July 2019.

16 Yu, J., Xie, J., Mao, X., Wang, M., Li, N., Wang, J., et al. (2011). Hepatotoxicity of major

17 constituents and extractions of Radix Polygoni Multiflori and Radix Polygoni

18 Multiflori Praeparata. *J. Ethnopharmacol.* 137, 1291–1299.

19 doi:10.1016/j.jep.2011.07.055.

6  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0

Yu, Z., Samavat, H., Dostal, A. M., Wang, R., Torkelson, C. J., Yang, C. S., et al.

(2017). Effect of Green Tea Supplements on Liver Enzyme Elevation: Results from a Randomized Intervention Study in the United States. *Cancer Prev. Res. (Phila)*. 10, 571–579. doi:10.1158/1940-6207.CAPR-17-0160.

Zhang, L., Liu, X., Tu, C., Li, C., Song, D., Zhu, J., et al. (2019). Components synergy between stilbenes and emodin derivatives contributes to hepatotoxicity induced by *Polygonum multiflorum*. *Xenobiotica* 50, 515–525. doi:10.1080/00498254.2019.1658138.

Zhu, Y., Niu, M., Wang, J.-B., Wang, R.-L., Li, J.-Y., Ma, Y.-Q., et al. (2018). Predictors of poor outcomes in 488 patients with herb-induced liver injury. *Turkish J. Gastroenterol.* 2018, 47–58. doi:10.5152/tjg.2018.17847.

Zhuge, Y., Liu, Y., Xie, W., Zou, X., Xu, J., and Wang, J. (2019). Expert consensus on the clinical management of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome. *J. Gastroenterol. Hepatol.* 34, 634–642. doi:10.1111/jgh.14612.

**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	<i>Aloe vera</i>	26/M	72	30	Digestive disorders	Infusion of herbs	Jaundice	None	CIOMS Probable	Argentina/ (Curciarello et al., 2008)
02	<i>Argemone mexicana L</i>	55/F	NA	NA	Digestive disorders	NA	Jaundice Rechallenge	None	CIOMS Highly Probable	Mexico/ (Meléndez González, 2013)
03	<i>Camellia sinensis</i>	43/F	240	225	Constipation	Infusion of herbs	Abdominal pain Fever	None	Karch-Lasagna: Problabe	Colombia/ (Muñoz et al., 2009)
04	<i>Centella asiatica</i>	61/F	30	30	Weight loss	Tablets unknown strength	Jaundice Choluria Hepatomegaly Arthralgia Hepatomegaly Rechallenge	None	NA	Argentina (Jorge OA and Jorge AD, 2005)
05	<i>Centella asiatica</i>	52/F	21	21	Weight loss	Tablets	Jaundice Choluria Hepatomegaly	None	NA	Argentina/

								Rechallenge			
06	<i>Centella asiatica</i>	49/F	60	60	Weight loss	Tablets	Jaundice Asthenia Hepatomegaly	None	NA		Argentina/ (Jorge OA and Jorge AD, 2005)
07	<i>Cochlospermum vitifolium</i>	25/F	120	120	Maintain Overall health	Infusion of herbs 500 mL	Jaundice	None	CIOMS probable		Mexico/ (Martínez- Rodríguez et al., 2015)
08	<i>Crotalaria juncea</i>	35/F	120	210	Arthralgia	2 L	Abdominal pain, Ascites Portal hypertension Cirrhosis Pregnancy at the time of HILI diagnosis	None	NA		Ecuador/ (Lyford et al., 1976)
09	Euforia®	45/F	NA	30	Weight loss	60 mL of Juice	Jaundice Fever	Levothyroxine Nifedipine	CIOMS Probable		Puerto Rico/ (Jiménez- Encarnación et al., 2012)

10	Herbalife®	52/F	30	NA	Weight loss	NA	NA	NA	CIOMS	Venezuela/
----	------------	------	----	----	-------------	----	----	----	-------	------------

10  
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

		used in 2013							Probable	(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)
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	<i>Hypericum perforatum</i>	79/F	NA	NA	NA	NA	Jaundice	<i>Copaifera langsdorfii</i> <i>Desf</i> Levothyroxine Ômega 3 Glucosamine	NA	Brazil/ (Agollo Costa et al., 2014)

									Condroitin		
16	Shen-Min®	28/F	56	51	Hair supplement	2 tablets	Jaundice Hepatomegaly	None	CIOMS Probable	Colombia/ (Cárdenas et al., 2006)	
17	Tiodrix HR®	63/M	49	45	Diabetic neuropathy	Tablets 600 mg	Fever Pruritus Rechallenge	Insulin valsartan levothyroxine	CIOMS Highly probable	Argentina/ (Ridruejo et al., 2011)	
18	<i>Ruellia bahiensis</i>	23/F	150	150	Digestive disorders	Infusion of herbs	Abdominal pain	Levonogestrel, Ethinily estradiol, prednisone, <i>Peumus boldus</i> , <i>Piper umberllatum</i>	Teschke, Schwarzenboeck and Hennermann's algorithm Possible	Brazil/ (Santos Júnior et al., 2018)	
19	<i>Camellia sinensis.</i>	2/M	150	150	Digestive disorders – substitute for milk	Infusion of herbs	NA	Amoxicillin for 7 days, one month before hospitalization	NA	Argentina/ (D'Agostino et al., 2019)	
20	<i>Carthamus tinctorius</i>	44/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/ (de Ataide et al., 2018)	
21	<i>Carthamus tinctorius</i>	66/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/ (de Ataide et al., 2018)	

22	<i>Carthamus tinctorius</i>	32/F	NA	NA	Weight loss	Oil	NA	NA	NA	Brazil/ (de Ataide et al., 2018)
23	<i>Piper methysticum</i>	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)

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

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®: Thiocetic Acid

7

8

**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	Total bilirubin (mg/dL)	ALT (UI/L)	ALP (UI/L)	Type Liver injury Liver Biopsy*	Hospitalization	Outcome
		<b>Services (MPNS)</b>						
01	<i>Aloe Vera</i>	Aloe vera (L.) Burm.f. [Asphodelaceae]	13.0	935	200	Hepatocellular	Yes	Resolved
02	<i>Argemona mexicana L</i>	Argemone mexicana L. [Papaveraceae]	2.5	211	434	Mixed	No	Resolved, 46 d
03	<i>Camellia sinensis</i>	Camellia sinensis (L.) Kuntze [Theaceae]	2.1	841	100	Mixed	Yes	Resolved, 4 d
04	<i>Centella Asiatica</i>	Centella asiatica (L.) Urb. [Apiaceae]	4.2	1193	503	Granulomatous acute hepatitis, marked cellular necrosis	No	Resolved, 60 d UDCA 10 mg/kg/day ASMA: 1/160 ANA: 1/320
05	<i>Centella asiatica</i>	Centella asiatica (L.) Urb. [Apiaceae]	19.9	1694	472	Chronic hepatitis with cholestasis, granulomas and	No	UDCA 10 mg/kg/day Normalization liver



							cirrhotic transformation		parameter , 60 d. 5-y follow-up
06	<i>Centella asiatica</i>	Centella asiatica (L.) Urb. [Apiaceae]	3.9	324	484	Granulomatous acute hepatitis with necrosis	No	Resolved, 30 d UDCA 10 mg/kg/day	
07	<i>Cochlospermum Vitifolium</i>	Cochlospermum vitifolium (Willd.) Spreng. [Bixaceae]	7.9	221	1201	Cholestasis Steatohepatitis with fibrosis	Yes	Resolved, 180 d ANA: 1:80	
08	<i>Crotalaria juncea</i>	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 Aito	17.6	837	134	Submassive necrosis	Yes	Resolved, 540 d ANA: 1:320	

8  
10  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
30  
1  
2  
3  
4  
5  
6  
7  
8

			n [Ericaceae], Punica granatum L. [Lythraceae], Camellia sinensis (L.) Kuntze [Theaceae], Morinda citrifolia L. [Rubiaceae], Lycium barbarum L. [Solanaceae]						
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	
15	<i>Hypericum perforatum</i>	Hypericum perforatum L. [Hypericaceae]	9.0	1667	NA	Hepatocellular	No	Resolved, 49 d	

16 Shen- Min®

*Copaifera langsdorffii* Desf.[Fabaceae]

*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*

8  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6

2.3      2922    153  
Hepatocellular  
Yes      Resolved,

2  
5  
d



23	<i>Piper methysticum</i>	Piper methysticum G. Forst. [Piperaceae]	12.40	NA	NA	Submassive necrosis	Yes	ALF, transplant
----	------------------------------	--	-------	----	----	------------------------	-----	--------------------

---

\* Liver biopsy findings are shown when available

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

Case n° 10 is included in the Latin America DILI Network database

Sinusoidal Obstruction Syndrome also known as Hepatic Veno-Occlusive Disease

16  
17  
18

**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*	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 <sup>#</sup>	22
Main herbs	Herbalife® products, <i>Camellia sinensis</i>		Herbal decoction with unknown constituents	Herbalife® products, <i>Centella asiatica</i> , <i>Carthamus tinctorius</i>

\*median, ND, no data

<sup>#</sup>including patients with sustained liver-related laboratory, radiologic, or histologic abnormalities at 6 months after HILI onset.

**Figure legends**

**Figure 1.** Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram

8  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0  
1  
2  
3  
4  
5  
6  
7  
8  
9  
0

Figure 1. PRISMA Flow Diagram

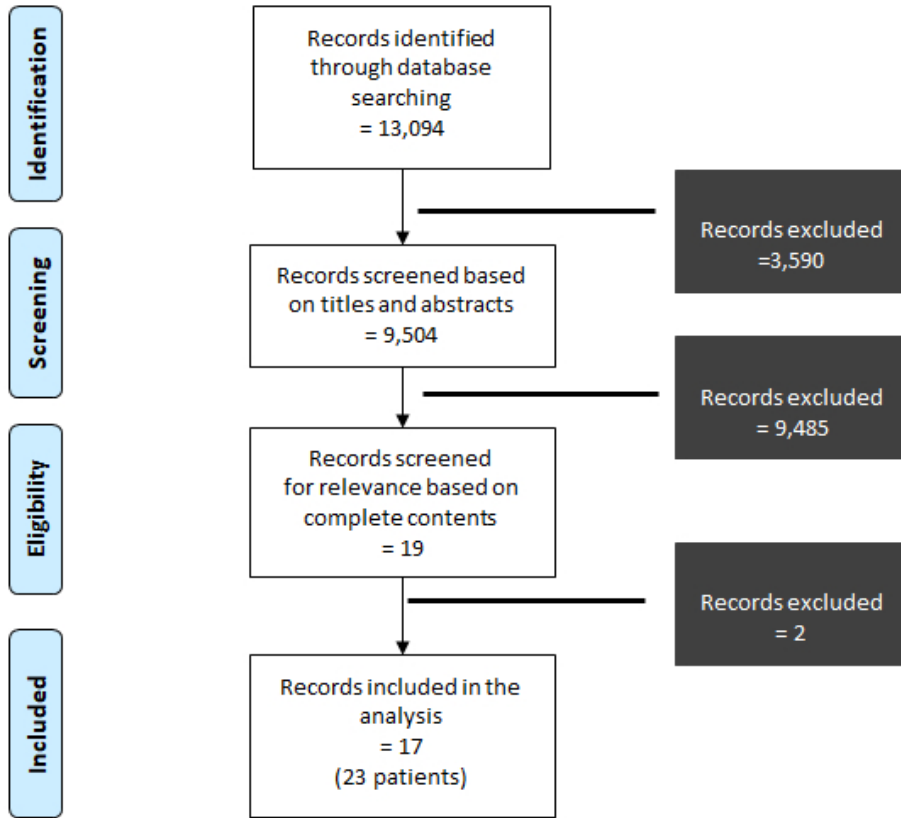


Figure 1. Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram

25x25mm (600 x 600 DPI)