



Original articles

Drug and herb-induced liver injury: A critical review of Brazilian cases with proposals for the improvement of causality assessment using RUCAM



Matheus William Becker^{a,*}, Michele John Muller Lunardelli^b, Cristiane Valle Tovo^c, Carine Raquel Blatt^d

^a Graduate Program in Medicine – Hepatology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

^b Pharmaceutical Services, Hospital Divina Providência, Graduate Program in Medicine – Hepatology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

^c Internal Medicine Department, Graduate Program in Medicine – Hepatology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

^d Pharmacoscience Department, Graduate Program in Medicine – Hepatology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil

ARTICLE INFO

Article history:

Received 8 May 2018

Accepted 8 February 2019

Available online 12 May 2019

Keywords:

Chemical and drug-induced liver injury

Pharmacovigilance

Pharmaceutical services

Adverse effects

ABSTRACT

Introduction and Objectives: Although hepatotoxicity accounts for 10% of adverse drug reactions, it remains poorly understood and underreported. This study aimed to summarize case reports of herb- and drug-induced liver injury in Brazil.

Methodology: Systematic review in the following databases: PubMed, SciELO, Science Direct, CAPES, and gray literature.

Results: Twenty-seven studies reporting 32 cases were identified. Brazilian cases were primarily detected in hospitals, and occurred mainly in young males suffering from chronic diseases. Drugs ($n = 29$) were a more frequent cause of liver injury than herbs ($n = 3$). Almost a third of these drugs were anticonvulsants, and 15 appear in the Brazilian List of Essential Medicines. In 50% of the cases, clinical manifestations started within 30 days of drug ingestion. Regarding the decline of liver enzymes, 50% of the cases reached normality after drug withdrawal. However, 7 deaths and 2 liver transplantations were reported. Only one study assessed causality using RUCAM.

Conclusion: Given the severe outcomes of DILI and HILI, early detection and management of hepatotoxicity to increase drug safety are necessary, as well as pharmacotherapeutic monitoring of patients with chronic diseases. Moreover, the application of the RUCAM algorithm in clinical practice has to be further disseminated.

© 2019 Fundación Clínica Médica Sur, A.C. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Drug-induced liver injury (DILI) is difficult to diagnose not only due to its similarity to viral hepatitis and other liver diseases, but also due to the lack of a confirmatory laboratory test. This means that the detection of this type of injury has a strong reliance on anamnesis, and its diagnosis is often obtained by exclusion [1].

In the United States, hepatotoxicity occurs in 10% of all adverse drug effect cases, in more than 50% of acute jaundice cases, and in 13–30% of acute liver failure cases [2]. Judging by case reports,

DILI can be considered a rare event, its frequency ranging from 1 in every 10,000 to 1 in every 100,000 adverse drug effect cases. However, since the number of patients involved in clinical studies is less than 10,000, pharmacovigilance studies are likely to detect hepatotoxicity [3,4].

In fact, the severity of hepatotoxicity has led regulatory agencies to withdraw several drugs from the market [5]. This goes to show the importance of pharmacovigilance studies and the need for proper reporting of adverse effects [6].

Direct toxicity is dose-dependent, reproducible, and has a predictable evolution. Idiosyncratic reactions manifest themselves after a period of latency, ranging from 5 to 90 days after drug ingestion. DILI is considered present when changes in hepatic markers are observed. It is classified as hepatocellular, cholestatic, or mixed, as indicated by the ratio between alanine aminotransferase (ALT) and alkaline phosphatase (AP) markers [7].

* Corresponding author at: Federal University of Health Sciences of Porto Alegre, R. Sarmiento Leite, 245 - Centro Histórico, Porto Alegre, Rio Grande do Sul, 90050-170, Brazil

E-mail address: matheuswbecker@gmail.com (M.W. Becker).

A recent literature review observed great discrepancies among Latin American case reports—between 2006 and 2012, Chile, Argentina, and Colombia were responsible for 91% of all published cases [8]. It is therefore reasonable to infer that in the remaining Latin American countries, DILI is considerably underreported. Uncoincidentally, although in 2010 the Brazilian Society of Hepatology warned that the number of DILI cases was growing, in this review only two Brazilian DILI research publications were identified [8]. In this context, there is an urgent need for alerting health managers about the importance of this topic, and for a proactive, countrywide scientific study of DILI [9].

The use of medicinal plants is customary in Brazil, usually lacking medical recommendation or prescription [10–12], since information on medicinal plants is rooted in traditional knowledge. Moreover, different studies point out to herb-induced hepatotoxicity as a common occurrence in several countries [13–15].

Considering the shortage of data on hepatotoxicity-inducing drugs and medicinal plants in the context of the Brazilian population, as well as the relevance of this topic, this study aims to identify the report profile of published Brazilian cases of drug- and herb-induced hepatic injury.

2. Methodology

A systematic review of Brazilian studies on drug and herb-induced liver injury was carried out. Searches were performed in the PubMed, SciELO, Science Direct, and CAPES databases.

Portuguese and English DILI descriptors were used in the search, according to the following syntax: (“Hepatotoxicity” or “drug induced liver injury” or “liver injury” or “hepatotoxic adverse drug”) and (“Brasil” or “Brazil” or “Brazilian”). All study designs were initially included, but for a better assessment of results, in this study only case reports were analyzed. The systematic review was recorded in the PROSPERO platform, under code CRD42017067817.

The selection was performed by two independent reviewers, in three sequential stages comprised of reading the title, the abstract, and then the full text. Disagreements were resolved by a third reviewer. Eligibility criteria were the following: being a Brazilian study, being a case report, and suspicion of DILI due to drug or herb use.

The following variables were analyzed: age; sex; patient's underlying disease; report location; drug; symptom onset time; length of hospital stay and normalization of liver enzymes; associated treatment; outcome; type of liver injury; use of algorithm to support diagnosis. Whenever possible, the liver injury was classified as hepatocellular, cholestatic, or mixed.

The collected data were compared to those of international studies [8,16–22]. A descriptive statistical analysis was performed using Excel 2013.

3. Results

A total of 337 records was initially identified. Among these, 264 were excluded during title and abstract screening, and the 73 remaining articles underwent a full-text review. Twenty-seven publications were case reports, describing a total of 32 DILI cases in Brazil [23–49]. Studies from 9 Brazilian states were found, with the state of São Paulo accounting for 41% of all studies. DILI identification occurred predominantly in hospitals ($n=28$). Average patient age was 27 years. Patients were older people (above 60 years old; $n=4$), adults (between 18 and 59 years old; $n=15$), and children (under 18 years old; $n=13$). Males accounted for 56% of the cases. Data on patients, drugs, clinical manifestation onset time, hospital length of stay, outcomes, and type of hepatic injury were summarized in Table 1.

Clinical outcomes were as follows: normalization of liver enzymes after medication interruption or change ($n=23$), jaundice ($n=14$), liver transplantation ($n=2$), and death ($n=7$). Fifteen liver biopsies were performed.

Patient deaths were associated with valproic acid ($n=2$), nimesulide ($n=1$), propylthiouracil ($n=1$), carbamazepine ($n=1$), lamotrigine ($n=1$), and gemtuzumab ($n=1$). Liver transplantation cases were associated with imatinib ($n=1$) and infliximab ($n=1$). Liver injuries were classified as hepatocellular ($n=8$), cholestatic ($n=11$), and mixed ($n=4$), or remained undetermined ($n=9$).

In 50% of the cases, clinical manifestation started within 30 days of drug ingestion. Regarding the decline of liver enzymes, in 50% of the cases normality was reached after drug withdrawal. This took up to 49 days. Enzyme rate normalization remained unreported in 15 cases, and clinical manifestation onset time remained unreported in 4 cases.

Several cases of DILI in chronic disease patients were reported. The most frequent chronic diseases were epilepsy ($n=8$) and hypothyroidism ($n=4$). Three authors reported algorithm support for DILI confirmation, and the identified algorithms were: Naranjo [50] 50 ($n=1$), Maria & Vitorino [51] ($n=2$), and RUCAM7 ($n=1$). Of the 20 drugs associated with DILI ($n=1$), Maria & Vitorino [51] ($n=2$) and RUCAM [7] ($n=1$), Maria & Vitorino [51] ($n=2$), and RUCAM. Among 21 medicines associated with DILI (Table 1), the most frequently occurring ones were valproic acid ($n=5$), propylthiouracil ($n=5$), carbamazepine ($n=3$), and *Senecio brasiliensis* ($n=2$). Anticonvulsants were associated with 28% of the cases. Fifteen (15) out of 21 liver injury-inducing drugs appear in the Brazilian List of Essential Medicines. Most of the cases were associated with drugs for primary pharmaceutical care ($n=18$), in comparison to specialized care ($n=5$) and strategic care ($n=3$).

Valproic acid was the drug most frequently associated with DILI ($n=5$, four children and one adult). Valproic acid-induced injuries were classified as cholestatic ($n=1$), mixed ($n=1$), or remained undetermined ($n=3$). Propylthiouracil was reported in 3 adult DILI cases (1 death) and in 2 cases involving children. Injuries caused by this drug were cholestatic ($n=4$). Carbamazepine-induced DILI occurred in three patients, causing cholestatic ($n=1$), mixed ($n=2$), or undetermined injuries ($n=1$).

4. Discussion

This is the first review of Brazilian DILI case reports. In the international literature, on the other hand, DILI case reports are easily identified [8,16,17,52,53]. Brazilian data, however, remain sparse. Considering the magnitude of the Brazilian population and the widespread use of drugs and medicinal plants known to induce liver injury, the fact that only 32 case reports were found points to alarmingly low rates of DILI suspicion and identification.

In a study on herb-induced liver injuries between 1999 and 2009 carried out by the Brazilian Health Surveillance Agency (ANVISA), only 10 cases of hepatotoxicity were reported [54]. None of these cases were found in our review.

Brazilian pharmacovigilance has been growing in the past two decades. In 2001, the creation of a sentinel network was proposed by ANVISA, in which reference hospitals cooperate to build a reliable information system, subsidizing the development of sanitary surveillance actions. In 2009, the Notivisa system was created, an online platform for adverse events notification [55]. Also, the Brazilian Society of Hepatology has the HEPATOX project, in which it is possible to notify case reports in an online database [56]. These efforts notwithstanding, adverse effects including hepatotoxicity remain underreported throughout Brazil.

In 2011, the Latin American DILI Network [57] was inaugurated for the prospective follow-up of DILI cases. The network was

Table 1

Characteristics of Brazilian case reports of drug-induced liver injury.

Author, date	Chronic disease	Medication and dosage	Symptom onset (Days)	Hospital admission (Days)	Enzyme normalization (Days)	Associated treatment	Outcome	Type of liver injury
Parra, 2015	Ulcerative colitis	Infliximab 5 mg/kg	126	NI	NA	NI	Transplantation	NI; extensive necrosis
Bernardes, 2015	Metastatic biliary adenocarcinoma	Nimesulide, NI	4	1	NA	Transfusion	Death	Cholestatic; inflammatory infiltrate, coagulative necrosis, and hepatocellular collapse
Agollo, 2014	Hypothyroidism	<i>Hypericum perforatum</i> , NI	NI	NI	49	None	Progressive reduction of enzymes	Hepatocellular
Bucaretychi, 2014	Newborn fever	Acetaminophen 10 mg/kg every 4 h for three days; total cumulative dose around 180 mg/kg	3	34	11	Infusion of N-acetylcysteine in 21 h (150 mg/kg in 60 min, 50 mg/kg in 4 h, 100 mg/kg in 16 h), maintained at 6.25 mg/kg/h until D11	Hospital infection by <i>Staphylococcus aureus</i> , oxacillin resistant, treated; clinical and laboratory parameters recovery	Hepatocellular
Almeida, 2013	Graves' disease	Propylthiouracil 1500 mg/day	21	60	NI	Dexamethasone 8 mg/day and propranolol up to 200 mg/day, plasmapheresis and total thyroidectomy, levothyroxine 200 µg	Multifactorial encephalopathy, but with good clinical evolution	Cholestatic
Beraldo, 2013	Hypertension, dyslipidemia,	Amoxicillin/clavulanate 500 mg three times a day for 21 days	24	30	120	Cholestyramine 4 g 6 h/6 h.	Normalized after medication was suspended	Cholestatic; Ductopenia, vacuolization, and hepatocyte necrosis; granulomatosis
Gaeti, 2013	Epilepsy	Carbamazepine 200 mg/day for 30 days	27	21	NI	Dexchlorpheniramine 2 mg OA 3×/day (13 days); Methylprednisolone EV 10 mg/kg (8 days); Prednisolone 1–2 mg/kg/day OA (11 days)	Normalized after medication was suspended	Cholestatic
		Phenytoin 100 mg two times a day for 15 days	7	30	NI	Acetaminophen 400 mg OA 6/6 h; Dexchlorpheniramine 2 mg 3×/day (3 days) OA; Hydrocortisone EV 10 mg/kg/day (12 days) and Prednisolone 1–2 mg/kg/day OA (6 days)	Normalized after medication was suspended	Cholestatic
Marques, 2012	Hansen's disease	Dapsone, rifampicin, and clofazimine, NI	30	NI	NI	NI	Normalized after medication was changed	Cholestatic
Volpato, 2011	Antiphospholipid syndrome	Methyldopa, NI	30	15	45	Hydralazine	Normalized after medication was changed	Hepatocellular
Haendchen, 2011	Systemic lupus erythematosus	Chlorine 150 mg twice a week and herbs	NI	NI	NI	NI	Normalized after medication was suspended	Mixed
Silva, 2010	Systemic lupus erythematosus	Enalapril 20 mg/day	30	26	180	NI	Normalized after medication was suspended	Cholestatic. periportal necrosis, sinusoidal fibrin deposition, ductal metaplasia with macro and micro-vesicular steatosis associated with necrophilia infiltration

Table 1 (Continued)

Author, date	Chronic disease	Medication and dosage	Symptom onset (Days)	Hospital admission (Days)	Enzyme normalization (Days)	Associated treatment	Outcome	Type of liver injury
Barbieri, 2010	Epilepsy	Carbamazepine, NI	120	NI	NA	NI	Bronchopneumonia, pulmonary hemorrhage, respiratory failure, and death Hemodynamic aggravation, with myoclonic convulsions, severe hypovolemic shock, and death	Mixed; irregular nodules cholestasis, peripheral and septal inflammatory process NI; biliary ductular fibrous proliferation pattern
		Valproic acid, NI	121	NI	NA	NI		
Rodrigues, 2010	Psoriatic arthritis	Isoniazid 300 mg/day	15	7	NI	NI	Normalized after medication was suspended	NI
Perini, 2009	Chronic myeloid leukemia	Imatinib 400 mg/day	NI	NI	NA	NA	Liver transplantation; therapy change (Nilotinib)	Hepatocellular; necrosis 85% liver, cholestasis, and ductular reaction
Batista, 2009	Ulcerative colitis	Sulfasalazine 4 g/day	42	3	NI	Prednisone 20 mg/day and ciprofloxacin 1 g/day	Normalized after medication was suspended	NI
Adriano, 2009	Manic depressive illness	Lamotrigine 50 mg/day	25	2	NI	Support for encephalopathy	Acute liver failure, multiple organ dysfunction, death	Mixed; inflammatory portal infiltrate in the hepatic duct and necrosis
Neves, 2006	Paranoid schizophrenia	Valproic acid 500 mg/day	28	NI	35	Electroconvulsive therapy	Normalized after medication was suspended	Mixed
		Clozapine 150 mg/day	42	NI	7	Electroconvulsive therapy	Normalized after medication was suspended	Hepatocellular
Amorim, 2005	Acne	Flutamide 250 mg/day	210	NI	71	NI	Normalized after medication was suspended	Hepatocellular
Massumoto, 2004	Acute myeloid leukemia	Gemtuzumab ozogamicin, NI	6	33	NA	Paracentesis, transfusion, laparotomy	Death	NI; hepatic veno-occlusive disease
Taniguchi, 2002	Asthma	<i>Senecio brasiliensis</i> tea 2 liters/day	28	35	NI	NI	Normalized after the use of the tea was suspended	NI; hepatic veno-occlusive disease
Ramos, 2002	Epilepsy	Carbamazepine 1200 mg/day	870	NI	810	NI	Partial reversion of ductopenia in 14 months; reduction of GGT	NI; ductopenia
Pereira, 2000	Tuberculosis	Isoniazid 20, Rifampicin 20, and Pyrazinamide 35 mg/kg/day	4	45	33	NI	Normalized after therapy change	NI; severe macrovesicular steatosis, granuloma
Parolin, 2000	Hyperthyroidism	Propylthiouracil 100 mg/day	450	>10	75	Propranolol 40 and Prednisone 60 mg/day	Normalized after therapy change	Cholestatic; hepatocyte ballooning and portal enlargement
Gonçalves, 1999	Hyperthyroidism	Propylthiouracil 600 mg/day	360	NI	35	NI	Normalized after therapy change	Cholestatic
		Propylthiouracil, NI	NI	NI	NI	NI	Death	Hepatocellular; hepatic necrosis
Magnabosco, 1997	Healthy	<i>Senecio brasiliensis</i> , NI	NI	25	180	Furosemide	Normalized after the use of the tea was suspended	NI, veno-occlusive disease
Antoniuk, 1996	Epilepsy and West syndrome	Valproic Acid 30 mg/kg/day	90	30	NA	NI	Death	NI
		Valproic Acid 37 mg/kg/day	180	>4	4	NI	Normalized after therapy change	Hepatocellular; hepatic necrosis
		Valproic Acid 45 mg/kg/day	360	>8	8	NI	Normalized after therapy change	Cholestatic
Hayashida, 1990	Newborn	Propylthiouracil 250 mg/day (placental pathway)	4	NI	90	NI	Normalization of enzymes after weaning	Cholestatic

NI: not identified; NA: does not apply; OA: oral administration.

modeled after similar endeavors in Spain [16] and Iceland [52], both based on RUCAM. A recent study by the LATINDILI group presented new data from Latin America, comprised of 250 DILI case records. Average age was 51 years (15–89 years), and the female sex was predominant (59%). Most DILI cases were from Argentina (47%), followed by Uruguay (32%), Chile (7%), Mexico (5%), Paraguay (3%), Venezuela (3%), Ecuador (2%), Brazil (0.5%), and Peru (0.5%) [58].

Reports found in our research were mostly identified in hospitals. This is to be expected, considering that hospitals have better diagnostic resources, as well as the possibility of multi-professional care, both of which may improve identification rates. Furthermore, health professionals who are involved in academic activities may be more encouraged to identify and publish DILI cases.

As shown in Table 2, few studies contain information on hospital length of stay. In those that do, hospitalization times were significantly longer in comparison to literature results. This comparison must be performed with caution, considering studies' methodological differences, but it is suspected that several DILI cases originate from outpatient prescriptions, and, due to DILI's acute characteristic, identification is only effectively carried out after hospital admission. The frequency of hospitalized patients with DILI in Iceland was 0.7% [52]. In a study in the United Kingdom, a 0.7% incidence of DILI was found in 1964 consecutive hospital admissions [59]. In Switzerland, a study with 4209 patients found an incidence of 0.7% admissions due to DILI, in addition to 1.4% patients who developed DILI while hospitalized. These studies also suggest high rates of underdiagnosis and underreporting, with no DILI diagnosis being obtained in 50% of cases [60]. While DILI does seem to have an impact on hospital admission, the number of patients hospitalized for other causes who developed DILI during hospitalization was twice as high as the number of patients initially hospitalized due to DILI. These results suggest that it may be important to carefully monitor patients' liver function, and also gather more data on potentially hepatotoxic drugs used in hospitals. Also, the use of RUCAM whenever DILI is suspected should be stimulated [7].

The regional coverage of the cases included 9 out of 26 Brazilian states, and almost half of the reported cases came from the state of São Paulo. This distribution may indicate that DILI health concerns have yet to reach several Brazilian regions, with many occurrences possibly neglected. Access to information as well as regional and cultural differences in the reporting of cases may bear on these results, once again reinforcing the central role of the publication and discussion of case reports, in order to assist in the diagnosis and management of similar cases.

Drug-induced liver injury is more common in adults, although the number of cases affecting children is also significant. The average age of DILI patients found in the literature is between 49 and 58 years. In Spain, nearly 50% DILI cases affect older people, with advanced age being regarded as an important predictor of hepatotoxicity. In Brazil, 12.5% of reported cases involved older people. Cholestasis was more strongly associated with advanced age, while hepatocellular injury was more strongly associated with the younger population [61,62], and this considerable age gap may be related to Brazil's socioeconomic profile as a developing country. However, case reports found in this review mostly regarded acute manifestations: chronic manifestations may be less attractive as a subject matter, which may have affected our results.

Hepatocellular injury was present in 35% of cases. A higher frequency was expected due to patients with this type of injury being younger and having a higher mortality rate (hepatocellular injury is more severe). The small rate of hepatocellular damage can be attributed to the unavailability of ALT or AP information in some cases' descriptions. Consequently, the relative frequency of this type of injury was inverted in comparison to international studies, with more cases of cholestatic injury, as shown in Table 2.

Jaundice, associated with advanced age, was present in 59% of the patients. The most severe cases of cholestatic injury were reported in young patients. When analyzing medications, age groups, and injury types, the data were similar to the literature's.

Anticonvulsant medicines were the most reported, contrasting with other studies, in which antibiotics and anti-inflammatory drugs were the most associated with cases of hepatotoxicity, as shown in Table 2 [16–20,63].

Children were more prone to liver injuries caused by valproic acid than adults; hepatocellular injuries were more frequent, but mixed and cholestatic injuries were also reported. A histological pattern of cholestasis with fibrotic lesions of ductile proliferation, with or without ductopenia, was found [64,65]. This suggests caution when administering valproic acid to children. Pediatricians should have a good grasp of the drug's hepatotoxic potential and develop protocols for early liver injury detection.

Cases involving propylthiouracil occurred in adults. One case stands out, in which the drug used by the mother induced liver injury in her newborn. The symptoms appeared at birth, associated with the placental pathway. After a favorable evolution, the newborn was inadvertently breastfed by the mother even after presenting symptoms of liver damage, compounded by the excretion of the drug through breast feeding. Propylthiouracil is considered safe in pregnant women, as long as the antithyroid dose is optimized to avoid fetal complications related to thyroid function. Even so, this case shows that it may be important for doctors accompanying pregnant women to attentively consider the hepatotoxic manifestations of drugs such as propylthiouracil, as well as understand their placental and breast milk excretion. In the abovementioned case, the injury pattern was cholestatic and the outcome was positive; another propylthiouracil case involving a hepatocellular injury, however, resulted in death. Histology for cases associated with this drug was compatible with that found in the literature, except for ballooning, which is characteristic of DILI and unrelated to propylthiouracil [66–68].

Carbamazepine is among the antiepileptic drugs most commonly associated with DILI. There are reports of cross-toxicity with phenytoin and lamotrigine. The injury often varies between the three types, but it is slightly more associated with chronic hepatitis; there are reports of ductopenia, eosinophilia, and granulomas, and, in some cases, steatosis [69,70]. In the Brazilian scenario, drug-induced liver injury in epileptic patients may have become a major issue. The need for combining various anticonvulsant medications can increase the odds of DILI; in fact, this study found that anticonvulsants were responsible for 28% of DILI cases and 57% of DILI deaths. Thus, it is abundantly clear that the more frequent use of hepatotoxic drugs by some specialties means that they must have precise knowledge of DILI.

Medicinal plants were responsible for three intoxication cases, two caused by the consumption of *Senecio brasiliensis*, and another by the consumption of *Hypericum perforatum* (also known as St. John's wort). Hepatotoxicity by herbal medicines may be more difficult to detect. Although the RUCAM algorithm can be used for both drugs and herbs, and is able to show the causality of a single chemical when used for drugs, the same is not true for herbs. Medicinal plants usually have many compounds, and properly investigating them is a much more involved process [7]. In the St. John's wort case, the authors suspected an interaction between *Hypericum* and copaiba oil (a resin oil extracted from the *Copaifera* sp. trunk and commonly used as an anti-inflammatory). However, they did not fully explain their suspicion and did not discuss other possibilities, such as levothyroxine, glucosamine, and chondroitin.

Our research group has recently published a Brazilian case report of liver transplantation by Kava [71]. The RUCAM resulted in a "probable" causality grading. The chemical profile of the sample used by the patient was investigated, and even though we were

Table 2

Comparison between Brazilian and international studies on drug-induced liver injury.

	Brazil	LATINDILIN	Sweden	Japan	Singapore	Spain	USA	Korea
Year	1990–2015	1996–2012	1975–2005	1997–2006	2004–2006	1994–2008	2004–2015	2005–2007
Number of cases	32	176	784	1676	31	867	899	371
Case design	Retrospective, published case reports	Retrospective, case reports	Government records	Multicentric, Retrospective	Population-based prospective	51 centers	Prospective 5 centers	Prospective 17 centers
Hepatocellular (%)	34 ^a	54	52	59	74	55	53	NI
Cholestatic (%)	39 ^a	27	29	21	19	25	23	NI
Mixed (%)	14 ^a	19	21	20	6	21	22	NI
Age average	27	55	58	55	51	54	49	49
Female (%)	44	67	57	57	45	49	59	63
Hospitalized (%)	87	NI	NI	NA	NI	59	55	100
Death or transplant (%)	28	14	9.2	3.7	9.6	5.4	10.2	1.3
Responsible agents (%)	Anticonvulsant drugs (28)	Anti-inflammatory drugs (34)	Antibiotics (27)	Antibiotics (14)	TCM (54)	Antibiotics (39)	Antibiotics (45)	Herbal medicines (27.5)

TCM: Traditional Chinese Medicine.

^a Considering the available data ($n = 23$).

unable to identify the specific substance responsible for the toxicity, potential alternatives were successfully excluded, such as fungal contamination and likely hepatotoxic compounds.

In herb-induced liver injury (HILI), causality is generally harder to define than in DILI. Reports of hepatotoxicity by *Senecio* spp. in humans are rare, and we were unable to find any other *Senecio brasiliensis* human case, although veterinarian cases have been reported. This herb seems to have no important indication for medicinal use, and is already recognized as toxic [72]. In any case, doctors should always investigate the traditional use of medicinal plants. HILI must be suspected when the patient reports using medicinal teas, since some patients tend to omit or fail to recognize the use of certain herbs as potential health hazards. Brazil is a major consumer of plants for therapeutic purposes and, according to the World Health Organization, up to 80% of the world population uses herbal medicines, mainly in developing countries [73]. In Asian countries, there has been a 19 to 63% increase in HILI cases [74]. Some studies have already pointed to HILI as the main cause of liver injury [20,21].

In this review, medicinal plants accounted for 9% of the case reports. This is similar to Spain's HILI rates, but lower than the United States', where plants and supplements are the second most frequent cause of liver injury, accounting for 16% of cases [16,17]. In Asian countries, plants and supplements are the leading cause of medicine-induced liver injury [14,20,21]. It is assumed that Brazil's rate may be higher than expected, due to the common consumption of medicinal plants, lack of knowledge about HILI, and underdiagnosis [10–12].

Only three studies reported using causality algorithms for DILI confirmation. This may be due to professionals lacking sufficient knowledge on this type of instrument. Algorithms are an important tool that can be helpful in collecting pertinent clinical information in order to accurately determine causality.

The use of causality algorithms is recommended by specialists, and the *Roussel Uclaf Causality Assessment Method* (RUCAM) is the most commonly applied variant [8,16,17,19,52]. Methods and strategies for detecting DILI should be widely disseminated, especially among general physicians, considering that, in most case reports, specialist follow-up showed that patients had developed chronic pathologies.

Most patients (84%) were diagnosed by exclusion of other diseases, without any mention of causality algorithms—the use of RUCAM retrospectively is not recommended, so causality cannot be determined post-diagnosis. This was a surprising result: although several suspected cases of hepatotoxicity were identified, the lack of information in these reports makes it impossible to determine causality. We believe this lack of information is due to subpar knowledge of DILI in Brazil, and also with the low quality and quantity of DILI researches in comparison to other countries. In both the medical and pharmaceutical fields, the country has no recognized DILI research groups, and, in this sense, the Latin American DILI research group is a welcome initiative—considering this study's results, we believe that Brazil could offer a much more significant contribution to DILI research. We are confident that the cooperation of Brazilian researchers with the LATINDILI network will favor the adequate use of RUCAM in case identification, so that future Brazilian cases can be integrated into the Latin American database.

Liver biopsy was reported in 47% of cases, and in some reports, it was referred to as an important confirmatory diagnostic method. However, considering DILI's inaccurate histological manifestations, which may lead to it being confused with primary liver and biliary diseases, there is no evidence that biopsy increases diagnostic accuracy. It is more commonly used for the exclusion of other diseases [74], and judiciously requested only for cases of greater severity and diagnostic difficulty. The RUCAM algorithm remains the best method for detecting DILI and determining its causality [75].

Some case reports lacked important information, such as: days elapsed since medication ingestion and symptom onset ($n = 1$), days of hospitalization ($n = 13$), and days until the normalization of hepatic enzymes ($n = 15$). These data should always be collected, since it contains important pieces of information for the determination of causality, epidemiological and economic impacts on the hospital network, and patient prognosis.

Medications associated with hepatotoxicity are included in the Brazilian List of Essential Medicines, which makes them accessible by most of the population. Although widely studied and known, these drugs can still pose risks. On the other hand, as their use increases, more information about these risks can be gathered and reported.

Prescription-free drugs, such as acetaminophen, have also been associated with hepatotoxicity. There are cases of acetaminophen use related to newborn fever and overdoses due to the prescription not being adjusted to the patient's weight. Pharmacist intervention during dispensation could prevent this type of problem, especially in Brazil, where the population has a large number of pharmacies at its disposal, but difficult access to the health system [76–78]. In this context, it is important to stimulate pharmacists to develop clinical and pharmacovigilance skills, mainly in community pharmacies. When pharmacists suspect DILI, they must refer the patient to a medical emergency service.

The promotion of health information to patients during drug dispensation is of great importance, since it can contribute to damage reduction and help include them in systems for pharmacovigilance and monitoring of adverse drug effects. In an Italian study, after a pharmaceutical intervention, the participation of patients in reports of adverse effects increased from 0% to about 7% [79]. In this regard, special attention should be given to prescription-free drugs, anti-inflammatory drugs, and medicinal plants, since these are easily accessible, widely used, and associated with high rates of self-medication [76].

Knowledge on relevant drugs, dosages, patterns of liver damage, and laboratory abnormalities is essential for the early detection of DILI cases, which can limit its impacts. A proactive stance by clinical pharmacists alongside health teams can favor early detection [80].

5. Conclusion

The worryingly low number of DILI case reports and the lack of knowledge on the topic stand out as this study's most relevant findings, showing the need to stimulate Brazilian DILI research and further the interactions between Brazilian researchers and the Latin American DILI network.

The populational profile of DILI case reports in Brazil is comprised of young males with chronic diseases. Despite the low number of reports, severe outcomes occurred in almost a third of the cases, pointing to a clear need for the early detection and management of DILI occurrences.

To this end, it is essential to disseminate knowledge on liver injury-inducing medications, DILI signs and symptoms, histology, serology of liver diseases, and the temporal relationship between drug administration and symptom onset. Moreover, RUCAM is an essential instrument in the confirmation of suspected induced liver injury cases. Strengthening the culture around DILI diagnosis and notification can increase professional and public knowledge, promoting drug safety in Brazil and worldwide.

Abbreviations

ALT	alanine aminotransferase
AP	alkaline phosphatase
CAPES	Coordination for the Improvement of Higher Education Personnel
DILI	drug-induced liver injury

HILI herb-induced liver injury
 RUCAM Roussel Uclaf Causality Assessment Method

Conflict of interest

The authors have no conflicts of interest to declare.

References

- [1] Teschke R, Frenzel C, Wolff A, Eickhoff A, Schulze J. Drug induced liver injury: accuracy of diagnosis in published reports. *Ann Hepatol* 2014;13:248–55.
- [2] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947–54.
- [3] Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. *Semin Liver Dis* 2002;22:145–55.
- [4] Björnsson E. Review article: drug-induced liver injury in clinical practice. *Aliment Pharmacol Ther* 2010;32:3–13.
- [5] Goldkind L, Laine L. A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: lessons learned from the bromfenac experience. *Pharmacoepidemiol Drug Saf* 2006;15:213–20.
- [6] Mota DM. Investigação em farmacoe epidemiologia de campo: uma proposta para as ações de farmacovigilância no Brasil. *Rev Bras Epidemiol* 2011;14:565–79.
- [7] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci* 2015;17.
- [8] Hernandez N, Bessone F, Sanchez A, di Pace M, Brahm J, Zapata R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. *Ann Hepatol* 2014;13:231–9.
- [9] Alves PRA. Reunião com Expertos em Hepatotoxicidade da Sociedade Brasileira de Hepatologia: Analgésicos, Antitérmicos, Insumos Vegetais, Fitoterápicos, Homeopáticos e AINES. *Revista Gastroenterologia Endoscopia Digestiva* 2011;30:47.
- [10] Schwambach K, Amador T. Estudo da Utilização de Plantas Medicinais e Medicamentos em um Município do Sul do Brasil. *Lat Am J Pharm* 2007;26:4.
- [11] Veiga Junior Vfd. Estudo do consumo de plantas medicinais na Região Centro-Norte do Estado do Rio de Janeiro: aceitação pelos profissionais de saúde e modo de uso pela população. *Rev Bras Farmacogn* 2008;18:308–13.
- [12] Araújo C. Perfil e prevalência de uso de plantas medicinais em uma unidade básica de saúde da família em Campina Grande. *Rev Ciênc Farm Básica* 2014;35:233–8.
- [13] Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana R, Grant L, et al. Liver injury from herbals and dietary supplements in the U.S Drug-Induced Liver Injury Network. *Hepatology* 2014;60:1399–408.
- [14] Zhou Y, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21,789 patients. *Eur J Gastroenterol Hepatol* 2013;25:825–9.
- [15] Stournaras E, Tziomalos K. Herbal medicine-related hepatotoxicity. *World J Hepatol* 2015;7:2189–93.
- [16] Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005;129:512–21.
- [17] Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. *Gastroenterology* 2015;148:1340–52, e7.
- [18] De Valle MB, Av Klinteberg V, Alem N, Olsson R, Björnsson E. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. *Aliment Pharmacol Ther* 2006;24:1187–95.
- [19] Takikawa H, Murata Y, Horiike N, Fukui H, Onji M. Drug-induced liver injury in Japan: an analysis of 1676 cases between 1997 and 2006. *Hepatol Res* 2009;39:427–31.
- [20] Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug-induced liver injury at an Asian center: a prospective study. *Liver Int* 2007;27:465–74.
- [21] Kim JB, Sohn JH, Lee HL, Kim J, Han D, Hahn J, et al. Clinical characteristics of acute toxic liver injury. *Korean J Hepatol* 2004;10:125–34.
- [22] Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-induced liver injury network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009;32:55–68.
- [23] Parra RS, Feitosa MR, Machado VF, Ramalho LN, da Rocha JJ, Feres O. Influximab-associated fulminant hepatic failure in ulcerative colitis: a case report. *J Med Case Rep* 2015;9:249.
- [24] Bernardes S, Souza-Nogueira A, Moreira E, Kishima M, Guembarovski A, Turini T, et al. Nimesulide-induced fatal acute liver failure in an elderly woman with metastatic biliary adenocarcinoma. A case report. *Sao Paulo Med J* 2015;133:371–6.
- [25] Agollo M, Miszputen S, Diamant J. Hepatotoxicidade induzida por *Hypericum perforatum* com possível associação a copaíba (*Copaifera langsdorffii* Desf): relato de caso. *Einstein* 2014;12:355–7.
- [26] Bucarechi F, Fernandes C, Branco M, De Capitani E, Hyslop S, Caldas J, et al. Acute liver failure in a term neonate after repeated paracetamol administration. *Rev Paul Pediatr* 2014;32:144–8.
- [27] Almeida R, Comarella A, Silveira M, Silva A, Casini A. Plasmáfereze pré-tireoidectomia em paciente com tireotoxicose e hepatotoxicidade por propiltiouracil: relato de caso. *Arq Bras Endocr Metab* 2013;57:322–6.
- [28] Beraldo D, Melo J, Bonfim A, Teixeira A, Teixeira R, Duarte A. Acute cholestatic hepatitis caused by amoxicillin/clavulanate. *World J Gastroenterol* 2013;19:8789–92.
- [29] Gaeti WP, Obreli-Neto PR, Moliterno RA, Schiavon GB, Cuman RK. HLA typing in Brazilian boys with aromatic antiepileptic drug-induced DRESS. *Int J Clin Pharm* 2013;35:319–22.
- [30] Marques G, Barreto J, Sousa J, Brandão L. Esquema alternativo para tratamento de Hanseníase multibacilar em um caso de hepatotoxicidade durante a poliquimioterapia. *Hansenol Int* 2012;37:4.
- [31] Volpato S, Losso C. Hepatite por metildopa em paciente portadora da síndrome antifosfolípide. *Rev HCPA* 2011;31:1.
- [32] Haendchen L, Jordão J, Haider O, Araújo F, Skare T. Porfíria cutânea tarda e lúpus eritematoso sistêmico. *An Bras Dermatol* 2011;86:173–5.
- [33] Da Silva G, Alves A, Duques P, Seva-Pereira T, Soares E, Escanhoela C. Acute hepatotoxicity caused by enalapril: a case report. *J Gastrointest Liver Dis* 2010;19:187–90.
- [34] Barbieri M, Silva L, Mattos A, Ferreira M. Lesão hepática grave induzida por fármacos anticonvulsivantes: relato de casos. *Rev Soc Bras Clín Méd* 2010; 8:2.
- [35] Rodrigues C, Vieira F, Callado M, Gomes K, Andrade E, Vieira W. Uso do abatacepte em uma paciente com artrite psoriásica. *Rev Bras Reumatol* 2010;50:340–5.
- [36] Perini G, Santos F, Funke V, Ruiz J, Neto B, Hamerschlag N. Nilotinib post-liver transplantation for acute hepatic failure related to imatinib. *Leukemia Res* 2009;33:234–5.
- [37] Batista R, Pozzobon B, Albuquerque I, Formiga G. Hepatotoxicidade induzida por sulfassalazina: relato de caso. *Rev Bras Coloproct* 2011;31:210–2.
- [38] Adriano A, Silveira J, Nogaara M, Siqueira M, Brandalise R. Insuficiência hepática aguda potencialmente induzida por lamotrigina: relato de caso. *Gastroenterol Endosc Dig* 2009;28:2.
- [39] Neves M, Kummer A, Luciano L, Laular H, Salgado J, Nicolato R, et al. Hepatotoxicidade grave secundária a psicofármacos e indicação de eletroconvulsoterapia a paciente com esquizofrenia. *J Bras Psiquiatr* 2006;55:74–7.
- [40] Amorim M, Amorim W, Duques P, Amorim P, Vasconcelos J. Hepatotoxicidade pela flutamida em paciente sob tratamento para acne: relato de caso. *An Bras Dermatol* 2005;80:381–4.
- [41] Massumoto C, Pinheiro R, Pinheiro Júnior E, Baiocchi O, Alves A. A rare case of fatal hepatic veno-occlusive disease and rupture of the spleen vein and artery after Gemtuzumab Ozogamicin (Mylotarg[®]) infusion. *Rev Bras de Hematol e Hemoter* 2004;26:218–20.
- [42] Taniguchi A, Célia L, Vieira S, Ferreira C, Zaffonato D, Cerski C, et al. Doença veno-oclusiva induzida por chá de senecio brasiliensis: relato de caso. *Revista HCPA* 2002;22.
- [43] Ramos A, Gayotto L, Clemente C, Mello E, Luz K, Freitas M. Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002;14:1019–22.
- [44] Pereira R, Tresoldi A, Hessel G. Insuficiência hepática pelo uso de isoniazida: relato de caso. *Arq Gastroenterol* 2000;37:72–5.
- [45] Parolin M, Lopes R, Telles J, Ioshii S, Hajar N. Hepatite aguda colestática pelo propiltiouracil: relato de caso. *Arq Gastroenterol* 2000;37:129–32.
- [46] Gonçalves Júnior J, Oliveira R, Carvalho A, Jorge P. Hepatite por propiltiouracil: apresentação de dois casos com evoluções diversas. *Arq Bras Endocr Metab* 1999;43:129–33.
- [47] Magnabosco E, Rivera M, Prolla I, Verney Y, Mello E. Doença veno-oclusiva hepática: relato de um caso. *J Pediatr (Rio J)* 1997;73:3.
- [48] Antoniuk S, Bruck I, Hönnicke L, Martins L, Carreiro J, Cat R. Insuficiência aguda hepática associada ao ácido valproico na infância: relato de três casos. *Arq Neuropsiquiatr* 1996;54:652–4.
- [49] Hayashida C, Duarte A, Sato A, Yamashiro-Kanashiro E. Neonatal hepatitis and lymphocyte sensitization by placental transfer of propylthiouracil. *J Endocrinol Invest* 1990;13:937–41.
- [50] Naranjo C, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
- [51] Maria V, Victorino R. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997;26:664–9.
- [52] Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013;144:1419–25.
- [53] Ghabril M, Bonkovsky H, Kum C, Davern T, Hayashi P, Kleiner D, et al. Liver injury from tumor necrosis factor-alpha antagonists: analysis of thirty-four cases. *J Gastroenterol Hepatol* 2013;11:558–64.
- [54] Balbino E, Dias M. Farmacovigilância: um passo em direção ao uso racional de plantas medicinais e fitoterápicos. *Rev Bras Farmacogn* 2010;20:992–1000.
- [55] Notivisa. Ministério da Saúde Agência Nacional de Vigilância Sanitária 2016; 2016. <http://www.anvisa.gov.br/hotsite/notivisa/apresenta.htm> [accessed 02.12.16].
- [56] Hepatox; 2016. <http://pesquisasbh.org/Protocolo/Hepatotoxicidade> [accessed 05.01.17].
- [57] Lucena MI, Cohen H, Hernández N, Bessone F, Dacoll C, Stephens C, et al. Hepatotoxicity, a global problem with local features: toward the creation of a Pan-American Hepatotoxicity Network. *Gastroenterol Hepatol* 2011;34:361–8.

- [58] Bessone F, Hernandez N, Lucena MI, Andrade RJ. The Latin American DILI registry experience: a successful ongoing collaborative strategic initiative. *Int J Mol Sci* 2016;17:313.
- [59] Meier Y, Cavallaro M, Roos M, Pauli-Magnus C, Folkers G, Meier P, et al. Incidence of drug-induced liver injury in medical inpatients. *Eur J Clin Pharmacol* 2005;61:135–43.
- [60] Duh MS, Walker AM, Kronlund Jr KH. Descriptive epidemiology of acute liver enzyme abnormalities in the general population of central Massachusetts. *Pharmacoepidemiol Drug Saf* 1999;8:275–83.
- [61] Björnsson ES. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. *Semin Liver Dis* 2014;34:115–22.
- [62] Lucena MI, Andrade RJ, Kaplowitz N, García-Cortés M, Fernández M, Romero-Gomez M, et al. Phenotypic characterization of idiosyncratic drug-induced liver injury: the influence of age and sex. *Hepatology* 2009;49:2001–9.
- [63] Bessone F, Sánchez HN, Di A, Gualano M, Arrese G, Ruiz M, et al. A comparative analysis of the Spanish and Latin-American prospective drug-induced liver injury (DILI) networks. *Hepatology* 2015;62:504.
- [64] Felker D, Lynn A, Wang S, Johnson DE. Evidence for a potential protective effect of carnitine–pantothenic acid co-treatment on valproic acid-induced hepatotoxicity. *Expert Rev Clin Pharmacol* 2014;7:211–8.
- [65] Gokce S, Durmaz O, Celtik C, Aydogan A, Gulluoglu M, Sokucu S. Valproic acid-associated vanishing bile duct syndrome. *J Child Neurol* 2010;25:909–11.
- [66] Lu R, Zhang Y, Tang F, Zheng Z, Fan Z, Zhu S, et al. Clinical characteristics of drug-induced liver injury and related risk factors. *Exp Ther Med* 2016;12:2606–16.
- [67] Tsutsui A, Nakanuma Y, Takaguchi K, Nakamura S, Shibata H, Baba N, et al. Comparison of liver biopsy findings with the Digestive Disease Week Japan 2004 Scale for diagnosis of drug-induced liver injury. *Mediators Inflamm* 2015;913793.
- [68] Sato I, Tsunekawa T, Shinohara Y, Nishio Y, Shimizu Y, Suzuki Y, et al. A case of autoimmune hepatitis with grave's disease treated by propylthiouracil. *Nagoya J Med Sci* 2011;73:205–9.
- [69] Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. *Liver Int* 2015;35:2343–53.
- [70] Grieco A, Forgione A, Miele L, Vero V, Greco A, Gasbarrini A, et al. Fatty liver and drugs. *Eur Rev Med Pharmacol Sci* 2005;9:261–3.
- [71] Becker M, Lourenço E, De Mello A, Branco A, Filho E, Blatt C, et al. Liver transplantation and the use of KAVA: case report. *Phytomedicine* 2018.
- [72] De Barros C, Driemeier D, Pilati C, Barros S, Castilhos M. *Senecio* spp. poisoning in cattle in southern Brazil. *Vet Hum Toxicol* 1992;34:241–6.
- [73] Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med* 2006;27:1–93.
- [74] Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014;89:95–106.
- [75] Teschke R, Frenzel C. Drug induced liver injury: do we still need a routine liver biopsy for diagnosis today? *Ann Hepatol* 2013;13:121–6.
- [76] Aquino DSd. Por que o uso racional de medicamentos deve ser uma prioridade? *Cien Saude Col* 2008;13:733–6.
- [77] Conselho Federal de Farmácia Dados 2015; 2015. <http://www.cff.org.br/pagina.php?id=801&menu=801&titulo=Dados+2015> [accessed 02.12.16].
- [78] Brasil. Resolução n 586 de 29 de agosto de 2013.Regulamenta as atribuições clínicas do farmacêutico e dá outras providências. In: Farmácia CFd, ed. 2013.
- [79] Parretta E, Rafaniello C, Magro L, Coggiola Pittoni A, Sportiello L, Ferrajolo C, et al. Improvement of patient adverse drug reaction reporting through a community pharmacist-based intervention in the Campania region of Italy. *Expert Opin Drug Saf* 2014;13:21–9.
- [80] Lunardelli MJM, Becker MW, Blatt CR. Hepatite medicamentosa: qual o papel do farmacêutico clínico? *RBFHSS* 2016;7:31–5.