

# Liver injury induced by herbal and dietary supplements: a pooled analysis of case reports

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**ABSTRACT – Background** – The intake of dietary supplements and medicinal plants is very popular worldwide. However, these products are not innocuous, and their intake can cause severe damage to health, especially liver injury. **Objective** – This study aims to describe the clinical cases of dietary supplements-induced liver injury (DSILI) and herb-induced liver injury (HILI), identifying the main products involved and the clinical outcomes related to them. **Method** – A literature search was performed in PubMed, EMBASE, Google Scholar, and LILACS databases, using the search terms: “Chemical and Drug-Induced Liver Injury”, “Dietary Supplements” and “Herbal” and their synonyms. **Results** – 189 articles were included in the study, totaling 428 clinical cases of drug-induced liver injury. The most frequent agents of liver injury were Herbalife® products, associated with 50 cases, Polygonum multiflorum, with 25 cases, Hydroxycut® products, and green tea, both associated in 19 cases, and Oxyelite Pro® and kava tea, both associated with 16 cases. Most individuals required hospitalization (82.6%) and an important number of cases evolved to death (3.6%), liver transplantation (8.9%), or chronic liver disease (1.9%). **Conclusion** – The indiscriminate use of dietary supplements and herbal products was associated with an alarming number of cases of liver injury. The mechanisms through which each of the products causes liver damage still need to be better understood, but this review is a warning about the risk associated with the use of products considered harmless by a large part of the population.

**Keywords** – Drug-Induced liver injury; hepatotoxicity; dietary supplements; herb-drug interactions.

## INTRODUCTION

The intake of dietary supplements has increased in recent decades and currently is very popular worldwide, especially in developed countries. The most recent data from the NHANES study, conducted in 2011–2012, showed that 52% of the North American population uses dietary supplements<sup>(1)</sup>. The medicinal use of plants is one of the oldest health practices of mankind, been used since the time of the Neanderthals<sup>(2)</sup>. Currently, this practice is known as phytotherapy and is very popular<sup>(3)</sup>. The WHO estimates that 80% of the world population uses phytotherapy<sup>(4)</sup>. There are many different types of dietary supplements for sale in different locations, including pharmacies, gyms, health food stores, and websites, and can be sold without a prescription from a physician or nutritionist<sup>(5)</sup>. One of the types of dietary supplements most sought after by consumers is products that promise to help with weight loss. The following stand out in this category: meal substitutes, which are usually presented in the form of shakes and soups, the most famous of which is known worldwide, Herbalife® products; products known as thermogenic which usually contain L-carnitine and/or caffeine associated with other components, such as Hydroxycut® and OxyElitePro® products; and products containing plant extracts such as green tea, white tea, guarana, *Garcinia Cambogia*, yerba mate, hibiscus, ginger<sup>(6)</sup>. Herbal products can be marketed for different therapeutic purposes: Black Cohosh, for example, is used to relieve menopausal symptoms<sup>(7)</sup>; Polygonum Multiflorum, to treat hair loss and prevent premature aging<sup>(8)</sup>; and *Aloe Vera* has

a variety of media effects, including the laxative and hypoglycemic effect<sup>(9)</sup>. Contrary to widespread belief, the consumption of dietary supplements and herbal products is not harmless. There are worrying associations between the use of dietary supplements with renal dysfunction<sup>(10,11)</sup>, heart problems<sup>(12)</sup>, and liver injuries<sup>(13)</sup>, which strengthens the importance of not underestimating the use of these products.

Drug-induced liver injury (DILI) is a liver problem caused by the use of medications, illegal drugs, herbal products, or food supplements<sup>(14)</sup>. Most products associated with DILI unpredictably generate the injury, regardless of the dose, by a multifactorial process that involves characteristics of the individual, the drug, and environmental factors, a condition called Idiosyncratic DILI, which makes the problem a major concern<sup>(15)</sup>. Liver injury induced by dietary supplements (DSILI) and liver injury induced by herbs (HILI) have been important parts of the cases of DILI<sup>(16)</sup>. In 2014, the incidence of DSILI and HILI was estimated to be 2.7 cases for 100,000 adults in the USA<sup>(17)</sup>. In South Korea, of the cases of hospitalization for liver toxicity, 23.1% were caused by herbs and dietary supplements<sup>(18)</sup>.

## METHODS

For this review, we performed a literature search in the databases PubMed, EMBASE, LILACS, and Google Scholar using the following keywords: “Chemical and Drug-Induced Liver Injury”, “Dietary Supplements”, “Herbal” and their synonyms, to identify

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tify case reports and case series of DSILI and HILI. DSILI were considered when the products involved contained micronutrients (mineral, or vitamins) or macronutrients (such as proteins), and HILI, when the products contained only herbs or plant extracts. The literature search was conducted from May 2021 to June 2021.

Studies were evaluated based on their titles and abstracts, and those eligible for the review were analyzed based on the full text. Case studies, published in Portuguese, English, or Spanish, were included. There was no limitation on the publication date and the age of individuals. Duplicate articles, animal studies, and cases of liver injury that were not associated with dietary supplements, herbal products, or steroids were excluded.

The data extracted from the studies were sex and age of individuals (in years); the product(s) associated with the liver injury; the composition of these products, when available; the daily dose consumed; latency (in weeks); the main symptoms and manifestations observed; tests that reflect liver function (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and total bilirubin (TB)); the type of liver injury; if the individual was hospitalized; the clinical outcome and time to the outcome, in weeks.

The composition of the products, when not described in the article, was searched on the internet (on reliable websites) when the name or brand of the product was reported. Latency was considered the period between the beginning of the product consumption and the onset of the first symptoms. The resolution was considered when the manifestations disappeared and the abnormal liver function markers returned to normal parameters, without liver transplantation; the chronic liver disease was established when the liver function markers remained elevated and/or the imaging examination indicated chronic injury for 6 months or more. The time to the outcome was considered the period between the diagnosis of liver injury and the occurrence of the outcome.

The cases were subdivided, based on the product's composition associated with the liver injury, into three categories: (1) cases associated with herbs or herbal products, when the only component(s) described in the consumed products consisted of some part of the plant(s), such as leaves and stem, or plant extract(s); (2) cases associated with dietary supplements, when the products associated with cases contained at least one type of nutrient; (3) and, cases associated with steroids, when the products mentioned contained some substance similar to testosterone, used to gain muscle mass. To obtain missing information, the corresponding author was contacted via email. Cases that followed with incomplete information were excluded from statistical analyzes.

### Statistical analysis

All statistical analyses were performed with SPSS (IBM®, version 26). The chi-square test was performed for categorical variables. The Shapiro-Wilk test was used to test the normality of continuous variables. The variables age, latency, liver test values (ALT, AST, ALP, GGT, TB), and time to the outcome, were analyzed using the non-parametric Kruskal-Wallis test and Pairwise method or test Mann Whitney U and expressed as median (interquartile range). A  $P$ -value  $<0.05$  was considered statistically significant.

## RESULTS

The search strategy retrieved 932 publications, and, after applying eligibility criteria, 189 articles were included in the study.

The articles were published between the years 1984 and 2021 and together totaled 428 cases of liver injury induced by dietary supplements, herbs, or steroids. Of these, 209 cases were associated with the consumption of herbal products, 202 associated with the consumption of s, and 17 were associated with the consumption of steroids. There has been an increase in publications related to this issue over time. The largest number of cases was published between 2003 and 2021 (89.9%).

TABLE 1 contains information from cases of liver injury induced by herbal products, dietary supplements, and steroids whose outcome was severe, such as death or liver transplantation. Complete information on all cases of liver injury induced by herbal products, dietary supplements, and steroids can be found in supplementary TABLES 1, 2, and 3, respectively. The main herbs associated with liver injury were: Polygonum Multiflorum, involved in 25 cases; green tea, 19 cases; kava (Piper methysticum) 16 cases; Chaparral (Larrea tridentata), 14 cases; *Aloe vera*, nine cases; Black Cohosh (Actaea pachypoda), eight cases; Valerian (Valeriana officinalis), six cases; Noni (Morinda citrifolia), six cases; Teucrium Polium, five cases; and Ashwagandha (Withania somnifera), five cases. Together, these herbs were responsible for 54.1% of the cases of hepatotoxicity related to herbal products. Other plants and herbs indicated in the cases were: Kratom (Mitragyna speciosa), yerba mate (Ilex paraguariensis), Artemisia annua, Teucrium viscidum, ginseng (Panax ginseng), green coffee (Coffea sp.), Eucalyptus (Eucalyptus), St. John's wort (Hypericum perforatum), cinnamon (Cinnamomum), artichoke (Cynara scolymus), yellow sweet clover (Melilotus officinalis), rooibos (Aspalathus linearis), garlic (Allium sativum), and senna (Senna alexandrina). These other plants represented 21.2% of the total cases of hepatotoxicity associated with herbal products. Herbal mix was considered when the patient consumed two or more herbs/plants during the same period. The cases of patients who consumed a mix of herbs represented 24.9% of cases of liver injury induced by herbal products. The main dietary supplements associated with liver injury were Herbalife® products, implicated in 51 cases; Hydroxycut®, in 19 cases; Oxyelite Pro® products, 16 cases; LipoKinetix®, eight cases; Move Free Advanced®, six cases, and Armolipid Plus®, five cases. Together, these dietary supplements represented 52.7% of the cases of hepatotoxicity related to dietary supplements. Various supplements, of different types and brands, such as supplements containing plant extracts, vitamins, and minerals; multivitamins; conjugated linoleic acid, and protein supplements for body mass gain such as creatine and protein shakes were included in the "other" category. Cases associated with consumption of these other dietary supplements represented 31.2% of supplement consumption. Poly-consumption was considered when the patient consumed two or more products, at least one of which was a supplement.

The demographic and clinical characteristics of cases are shown in TABLE 2, categorized by the type of product consumed. The median age of individuals who consumed herbal products was significantly higher than those who consumed dietary supplements ( $P=0.001$ ) and steroids ( $P=0.001$ ). There was a predominance of females (64.9%), except in cases of steroid use, in which all cases were male ( $P<0.001$ ). The median latency was significantly lower in cases of herbal product consumption compared to cases of dietary supplement consumption ( $P=0.021$ ). The individuals who consume dietary supplements presented more abdominal pain ( $P=0.047$ ) and nausea and vomiting ( $P<0.001$ ) compared to individuals in the other groups, likewise, pruritus was more associated with ster-

**TABLE 1.** Cases of liver failure associated with consumption of the most frequent dietary supplements and herbal products found in scientific literature.

Author/Year	Sex/ age	Product (s)	Daily dose	Latency (weeks)	Clinical presentations	Elevated liver markers	Type of liver injury	Outcome
Sheikh, 1997 <sup>(19)</sup>	F/59	Chaparral capsules	1800 mg	52	Abdominal pain, nausea/vomiting, jaundice, dark urine, light stools	ALT, AST, ALP, TB	Cholestatic	Transplant
Chow, 2008 <sup>(20)</sup>	F/51	Preparation of black cohosh	40 mg	8	Weakness, nausea/vomiting, jaundice, ascites	ALT, AST, ALP, GGT, TB	Hepatocellular	Transplant
Lynch, 2006 <sup>(21)</sup>	F/54	Black Cohosh	1000 mg	34	Weakness, encephalopathy	ALT, AST, ALP, GGT, TB	Mixed	Death
Jung, 2011 <sup>(22)</sup>	M/57	Polygonum multiflorum	UN	4	Fever, jaundice, encephalopathy	ALT, ALP, TB	Mixed	Death
Jung, 2011 <sup>(22)</sup>	M/24	Polygonum multiflorum	UN	2	Jaundice	ALT, ALP, TB	Hepatocellular	Transplant
Becker, 2019 <sup>(23)</sup>	F/45	Kava herb	100 mg	7	Nausea/vomiting, Jaundice, encephalopathy	ALT, AST, TB	Hepatocellular	Transplant
Campo, 2002 <sup>(24)</sup>	F/14	Preparation of Kava	NI	13	Nausea/vomiting, weakness	ALT, AST, GGT, TB	Hepatocellular	Transplant
MMWR, 2002 <sup>(25)</sup>	F/14	Kava Products	4 caps	17	Nausea/vomiting, jaundice, weakness	ALT, AST, GGT, TB	Hepatocellular	Transplant
Escher, 2001 <sup>(26)</sup>	M/50	Capsules of kava extracts	4 caps	8	Jaundice, weakness, dark urine, encephalopathy	ALT, AST, ALP, GGT, TB	Hepatocellular	Transplant
Teschke, 2008 <sup>(27)</sup>	F/60	Kava extract	UN	52	Abdominal pain, jaundice, weakness	UN	Mixed	Transplant
Teschke, 2008 <sup>(27)</sup>	M/50	Kava extract	UN	8	Abdominal pain, jaundice, weakness	UN	Hepatocellular	Transplant
Fong, 2010 <sup>(28)</sup>	M/20	Hydroxycut	UN	13	Nausea/vomiting, jaundice, weakness, encephalopathy	ALT, AST, TB	UN	Death
Fong, 2010 <sup>(28)</sup>	NI/NI	Hydroxycut	UN	52	Nausea/vomiting	ALT, AST, ALP, TB	Hepatocellular	Transplant
Fong, 2010 <sup>(28)</sup>	NI/NI	Hydroxycut	UN	8	Abdominal pain, nausea/vomiting, weakness	ALT, AST, ALP, TB	Hepatocellular	Transplant
Fong, 2010 <sup>(28)</sup>	NI/NI	Hydroxycut	UN	4	Nausea/vomiting, weakness	ALT, AST, ALP, TB	Hepatocellular	Transplant
Elinav, 2007 <sup>(29)</sup>	F/33	Protein mix drink, Herbalifeline (fish oil concentrate), Thermojetics herbal mix (tea), Thermojetics Green and beige capsules (herbal extract), Tang Kuei Plus, Instant drink with plant extracts, Sesame and Herbs tablets, Safflower oil capsules	UN	13	Jaundice, weakness	UN	Hepatocellular	Transplant
Favreau, 2002 <sup>(30,31)</sup>	F/20	Lipokinetix	UN	2	Abdominal pain, fever, jaundice, encephalopathy	ALT, AST, TB	Hepatocellular	Transplant
Scott, 2003 <sup>(32)</sup>	F/24	Lipokinetix	UN	13	Nausea/vomiting, jaundice, encephalopathy	ALT, AST, TB	Hepatocellular	Transplant
Neff, 2004 <sup>(33)</sup>	F/32	Lipokinetix	UN	2	UN	ALT, AST, TB	Hepatocellular	Transplant
Foley, 2014 <sup>(34)</sup>	F/45	OxyELITE Pro	UN	104	Jaundice, weakness, encephalopathy	ALT, AST, ALP, TB	UN	Transplant
Foley, 2014 <sup>(34)</sup>	M/28	OxyELITE Pro	UN	8	Jaundice, weakness encephalopathy	ALT, AST, TB	UN	Transplant
Roytman, 2014 <sup>(35)</sup>	M/22	New OxyElite Pro	UN	2	Abdominal pain, nausea/vomiting, jaundice, weakness, encephalopathy	ALT, ALP, TB	UN	Transplant
Roytman, 2014 <sup>(35)</sup>	F/48	New OxyElite Pro	UN	4	Abdominal pain, nausea/vomiting encephalopathy	ALT, ALP, TB	UN	Death
Johnston, 2016 <sup>(36)</sup>	F/42	New OxyELITE Pro	UN	UN	Nausea/vomiting, encephalopathy	ALT, AST, ALP, TB	UN	Death
Roytman, 2014 <sup>(35)</sup>	F/31	New OxyElite Pro; Garcinia Cambogia; Cellucor Super HD; HCA Supreme	UN	4	Nausea/vomiting weakness, jaundice, encephalopathy	ALT, ALP, TB	UN	Transplant
Heidemann, 2016 <sup>(36)</sup>	F/46	OxyELITE Pro; Stacker	1 cap	17	Jaundice	ALT, ALP, TB	Hepatocellular	Transplant
Heidemann, 2016 <sup>(36)</sup>	M/36	OxyELITE Pro; Ravage; Hydroxycut	3 cap	31	Jaundice	ALT, ALP, TB	Hepatocellular	Transplant
Sheikh, 1997 <sup>(19)</sup>	F/38	Chaparral capsules; multivitamins; folic acid; calcium	UN	UN	UN	TB	UN	Transplant
Perera, 2013 <sup>(37)</sup>	M/35	anabolic steroid; T propionate; nandrolone decanoate, L-glutamine; leucine, protein powder; vitamin C; zinc	UN	UN	Abdominal pain, Nausea/vomiting, jaundice, pruritus	AST, ALT, ALP, GGT, TB	Mixed	Death

<sup>1</sup>chi-square test; <sup>2</sup>Kruskal-Wallis test; <sup>3</sup>Mann Whitney Test. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TB: total bilirubin; GGT: gamma glutamyl transferase; UN: unavailable; Cap: capsule.

**TABLE 2.** Characteristics of liver failure cases, associated with the consumption of dietary supplements and herbal products, taken from the scientific literature, according to the type of the products.

	Herbal products (n=209)	Dietary supplements (n=202)	Steroids (n=17)	Total (N=428)	P-value
Age (Years)	49 (39–60)	42 (31–53)	31 (26–37.5)	45 (33–56)	<0.001 <sup>2</sup>
Sex (male), n (%)	67 (32.4)	62 (32.3)	17 (100)	146 (35.1)	<0.001 <sup>1</sup>
Hospitalization, n (%)	137 (84.6)	110 (78.6)	14 (100)	261 (82.6)	0.079 <sup>1</sup>
Latency (weeks)	6 (3–13)	8 (4–18.5)	7 (4–12)	7 (4–16)	0.016 <sup>2</sup>
<b>Clinical Presentations</b>					
Nausea/vomiting, n (%)	44 (21.9%)	56 (41.8%)	2 (11.8%)	102 (29%)	<0.001 <sup>1</sup>
Pruritus, n (%)	18 (9%)	24 (17.9%)	12 (70.6%)	54 (15.6%)	<0.001 <sup>1</sup>
Abdominal pain, n (%)	57 (28.4)	50 (37.3)	2 (18.8)	109 (31)	0.047 <sup>1</sup>
Dark urine, n (%)	38 (18.9)	21 (15.7)	4 (25.3)	63 (19.7)	0.619 <sup>1</sup>
Light Stools, n (%)	20 (10)	10 (7.5)	4 (23.5)	34 (9.7)	0.105 <sup>1</sup>
Fever, n (%)	20 (10)	15 (11.2)	1 (5.9)	36 (10.2)	0.778 <sup>1</sup>
Jaundice, n (%)	126 (62.7)	92 (68.7)	13 (76.5)	231 (65.6)	0.333 <sup>1</sup>
Encephalopathy, n (%)	8 (4)	16 (11.9)	2 (11.9)	26 (7.4)	0.019 <sup>1</sup>
Ascites, n (%)	7 (3.5)	3 (2.2)	0 (0)	10 (2.8)	0.615 <sup>1</sup>
<b>Liver parameters</b>					
ALT (U/L)	1123 (520–1752)	1320 (370–2343)	236 (116–575)	1146 (370–2036.2)	<0.001 <sup>2</sup>
AST (U/L)	926 (293.5–1557)	1062 (233.5–1861)	139 (80–332)	932.5 (226–1653.2)	0.006 <sup>2</sup>
ALP (U/L)	197.5 (151.5–308.5)	200(144–302)	155.5 (116.2–336.2)	198 (145.5–304.5)	0.560 <sup>2</sup>
GGT (U/L)	196 (121–365)	252 (109–370)	142 (72–382)	196 (110–368)	0.593 <sup>2</sup>
TB (mg/dL)	9.25 (2.9–17.6)	11.5 (3.75–22.2)	10.82 (5.53–20.65)	10.4 (3.5–19.4)	0.274 <sup>2</sup>
<b>Type of liver injury</b>					
Hepatocellular, n (%)	87 (59.2)	94 (71.2)	1 (7.1)	182 (62.1)	<0.001 <sup>1</sup>
Cholestatic, n (%)	27 (18.4)	20 (15.2)	12 (85.7)	59 (20.1)	
Mixed, n (%)	33 (22.4)	14 (10.6)	1 (7.1)	48 (16.4)	
Veno occlusive, n (%)	0 (0)	2 (1.5)	0 (0)	2 (0.7)	
Hepatoportal sclerosis, n (%)	0 (0)	2 (1.5)	0 (0)	2 (0.7)	
<b>Time to Outcome (weeks)</b>					
Recovered	8 (4–12)	8 (4–12)	13 (4–15)	8 (4–13)	0.293 <sup>2</sup>
Transplant	4 (1–7)	2.5 (1.25–5)	–	3 (1–5.5)	0.702 <sup>3</sup>

<sup>1</sup>chi-square test; <sup>2</sup>Kruskal-Wallis test; <sup>3</sup>Mann Whitney Test. ALT: alanine aminotransferase, AST: aspartate aminotransferase; ALP: alkaline phosphatase, TB: total bilirubin; GGT: gamma glutamyl transferase.

**TABLE 3.** Clinical evolution of liver failure cases, associated with the consumption of dietary supplements and herbal products, taken from the scientific literature, according to the composition of the products.

Products	Latency (weeks)	Hospitalization (%)	Encephalopathy (%)	Ascites (%)	Recovered (%)	Transplant (%)	Chronic (%)	Death (%)
<i>Camellia sinensis</i> (n=16)	6 (4–16)	69.2	0	0	94.4	0	5.6	0
<i>Aloe vera</i> (n=9)	8 (4–23)	88.9	0	11.1	100	0	0	0
Chaparral (n=13)	8 (5–16)	66.7	0	7.7	85.7	14.3	0	0
Black Cohosh (n=8)	17 (2.5–34)	66.7	12.5	0	87.5	0	0	12.5
<i>Polygonum multiflorum</i> (n=25)	4 (1–8)	96	4	0	92	4	0	4
Kava (n=15)	10.5 (5.2–17)	83.3	12.5	0	62.5	37.5	0	0
Ashwagandha (n=5)	2 (1–14)	ND	0	0	100	0	0	0
Teucrium Polium (n=5)	8 (3–20)	100	0	0	80	20	0	0
Noni Juice (n=6)	2 (1.5–6)	60	0	0	100	0	0	0
Herbal Mix (n=44)	5 (3–8)	90.9	5.9	9.8	84.6	7.7	0	7.7
Armolidip Plus® (n=6)	7.5 (3.5–19)				100	0	0	0
Herbalife® (n=50)	17 (9.5–52)	67.9	4.3	0	91.7	4.2	4.2	0
Lipokinetix® (n=6)	3.5 (2–7.5)	60	33.3	0	62.5	37.5	0	0
OxyElite Pro® (n=16)	6 (3–52)	81.3	40	0	56.3	18.8	12.5	12.5
Hydroxycut® (n=19)	8 (4–10)	88.2	5.9	0	78.9	15.8	0	5.3
Polyuse (n=34)	4 (4–16)	87	9.1	2	74.2	19.4	0	6.5
Move Free (n=63)	3 (2.7–9.7)	50	0	2.7	100	0	0	0
Steroids (n=15)	7 (4–12)	100	11.8	0	88.2	0	5.9	5.9
<b>P-value</b>	<0.001 <sup>2</sup>	0.006 <sup>1</sup>	0.015 <sup>1</sup>	0.404 <sup>1</sup>		0.048 <sup>1</sup>		

ND: no data. <sup>1</sup>chi-square test; <sup>2</sup>Kruskal-Wallis test.

oid use ( $P < 0.001$ ). The hepatocellular injury was associated with dietary supplement consumption, while the cholestatic injury was associated with steroid use, and the presence of both injuries was associated with herbal product consumption ( $P < 0.001$ ). The median levels of serum ALT ( $< 0.001$ ) and AST ( $P = 0.006$ ) were significantly lower in cases of steroid use. Encephalopathy was more associated with dietary supplements, being present in 16 cases ( $P = 0.019$ ).

TABLE 3 describes the clinical characteristics of cases related to the product consumed. The latency of cases of hepatotoxicity associated with consumption of Herbalife® products was significantly higher than the latency of cases of hepatotoxicity associated with the consumption of Noni ( $P = 0.034$ ), LipoKinetix® ( $P = 0.022$ ), Polygonum multiflorum ( $P < 0.001$ ), Herbal mix ( $P < 0.001$ ) and associated with the poly-consumption of supplements ( $P = 0.036$ ).

Observing the severity of cases related to the product consumed, encephalopathy was more associated with the consumption of LipoKinetix® and Oxyelite Pro®. Thirty-three percent of the individuals who consumed LipoKinetix® and 40% of the individuals who consumed Oxyelite Pro® had some degree of encephalopathy ( $P = 0.023$ ). Among cases associated with the consumption of Oxyelite Pro®, 18.8% underwent liver transplantation and 12.5% died or became chronic liver patients. Thirty-seven percent of individuals who consumed Lipokinetix®, 37.5% who consumed Kava, and 19.4% associated with poly-consumption required liver transplantation, showing a significant difference from the other groups ( $P = 0.048$ ). Hospitalization was less associated with cases of Move Free® consumption compared to other cases.

## DISCUSSION

The present study found 428 cases of liver injury associated with the consumption of dietary supplements, herbal products, and steroids, published in the scientific literature. The number of cases raised in the last two decades can be a response to the increased use of dietary supplements and, also, the greatest interest from health professionals on the subject, which leads to a further investigation.

Other studies also show the increase in cases of DSILI and HILI, over the years. Navarro et al.<sup>(38)</sup> investigated cases of hepatotoxicity reported in reference centers in the USA and observed an increase from 7% to 20% of DILI associated with dietary supplements and herbs between the years 2004 and 2013. Begotti, Sato, and Santiago<sup>(39)</sup> reviewed the literature and observed that 92% of hepatotoxicity reports associated with the use of herbal and dietary supplements were published between 2004 and 2015.

The literature search was focused on cases involving dietary supplements and herbs, which explains the low frequency of cases related to the use of steroids found in this review. Most cases involving the use of steroids were presented as dietary supplements, which unfortunately is common within the sports supplement market<sup>(40)</sup>. Possibly, if the term steroids had been added in the search, the frequency of these cases would be higher, since the steroid hepatotoxicity is already well established<sup>(41)</sup>.

The cases were divided based on the composition and description of the products involved in three categories: herbal products, dietary supplements, and products containing steroids. However, several dietary supplements contain plant extracts, implicated in cases of liver injury associated with herbal products, which complicates the identification of the most harmful product, since their effects can overlap. Several Herbalife® products, the most frequent in the dietary supplement category, are composed of a combination

of micronutrients, such as chromium, zinc, and vitamins with plant extracts, such as Camellia sinensis extract, Garcinia cambogia, Gymnema Sylvestre leaf extract, kava extract, the extract of Panax ginseng, Ilex Paraguariensis and *Aloe vera*. Another example that can be cited is the Hydroxycut® products, which contain, among other components, Garcinia cambogia, Gymnema Sylvestre, Camellia sinensis, and Yohimbe bark extract. This leads us to believe that more important than looking at the product name is looking at its composition since many common components in dietary supplements and herbal products are already well established as hepatotoxic.

The median age of the individuals reported in the cases was 45 (33–56) years. Hou, Zeng, and Wang<sup>(42)</sup>, when investigating the characteristics of 131 individuals hospitalized for liver injury induced by herbal medicines in China, identified a median age of 51 (13–86) years in the studied group. Hillman et al.<sup>(43)</sup> investigated the clinical and demographic characteristics of liver injury cases associated with dietary supplements and herbs and found a median age of 41 years. More importantly, our results indicated that individuals who consumed herbal products were older than individuals who consumed dietary supplements and products containing steroids. The medicinal use of plants increases with advancing age, in contrast to the consumption of supplements, which is more popular with young people, especially gym-goers who seek alternatives to improve performance and obtain better aesthetic results<sup>(44,45)</sup>.

The female gender was the most frequent among cases of liver injury, as well as the hepatocellular type injury. Byeon et al.<sup>(46)</sup> carried out a systematic review to determine the clinical characteristics of cases of herb-induced liver injury and observed that women and hepatocellular injury were the most prevalent among cases of HILI. Lee et al.<sup>(47)</sup> conducted a systematic review of cases of HILI in Korea and observed a prevalence of hepatocellular lesions, however, they did not observe a difference between gender.

The latency found in our results was 7 (4–16) weeks. We found that herbal products seem to cause liver injury faster than dietary supplements, but due to a lack of data, it was not possible to clarify which factors could be related to this result.

The serum levels of the hepatic markers were extremely high, characterizing a severe hepatic impairment. Compared to normal values, the medians of ALT, AST, and total bilirubin were elevated to 29, 23, and 9 times, respectively. As expected, the transaminases of cases associated with steroid use, which showed the prevalence of cholestatic lesions, showed significantly lower levels than in the other cases. However, surprisingly, there was no significant difference in serum levels of FA and GGT in the group of steroid use.

Based on our findings, it can be considered that a significant portion of cases of liver injury was severe. In most reports, individuals required hospitalization (84.6%). Hepatic encephalopathy or ascites, which are complications resulting from liver failure, were present in 10.2% of the individuals. From the cases included in this review, 14.4% of individuals did not recover completely from liver injury, and of that percentage, 15 individuals died, and 37 required liver transplantation. Zhu et al.<sup>(48)</sup> evaluated clinical characteristics of cases of liver injury associated with Chinese herbal medicine and found a similar percentage of cases with a poor prognosis: 16.7% of the cases did not progress to complete resolution of the liver injury, with 12.9% progressing to chronic liver injury; 0.6% of the individuals underwent liver transplantation and 3.2% died. Zhu et al.<sup>(49)</sup> observed in a retrospective cohort of patients hospitalized for HILI that 3.9% of the individuals

died, 14.9% developed chronic liver disease, and 0.2% underwent liver transplantation. Teschke<sup>(50)</sup> concluded in his review on liver injury induced by herbal medicines that some herbal products can generate serious liver injuries, including lethal cases and the need for liver transplantation. Several products have been implicated in cases of hepatotoxicity, however, some seem to provoke more serious injuries than others. In this study, it was observed that the product Oxyelite Pro<sup>®</sup> was associated with two cases of death, three cases of liver transplantation, and two cases of chronic liver disease, which represents 43.8% of the cases of liver injury involving the product. Liver transplantation was performed in three individuals who consumed Lipokinetix<sup>®</sup> and in six individuals who used kava. In 2013, USP Labs, manufacturer of OxyElite Pro<sup>®</sup>, reformulated the composition of its products, removing the ingredient 1,3-dimethylamylamine (DMAA) associated with outbreaks of liver and kidney injuries, and coronary disease, after notification from the FDA<sup>(51)</sup>. However, most of the injury cases associated with OxyElite Pro<sup>®</sup> included in our review did not have DMAA in its composition, which indicates that the problem was not resolved with the removal of this compound.

The doses observed in the cases varied widely, presenting several pharmaceutical forms, such as capsules, leaves, and infusion, which prevented a dose-effect evaluation. Although most cases of DILI are considered idiosyncratic, that is, they occur regardless of the dose, there are case reports in the literature of injury involving herbs of the intrinsic type, which occurred due to the consumption of high doses of the compound<sup>(52)</sup>.

Although the mechanisms by which liver injury induced by herbs and dietary supplements occurs are not clear, the presence of hepatotoxins in some plants and their extracts has already been identified<sup>(53)</sup>. Green tea contains phenolic compounds known as catechins, which are responsible for their antioxidant and beneficial effects, however, under certain conditions, catechins, especially epigallocatechin-3-gallate (EGCG), can be pro-oxidant, causing damage to the liver cell<sup>(54)</sup>. In *Polygonum multiflorum*, compounds known as anthraquinones have been identified as promoting liver injury by inhibiting proton transport, inhibiting bile acid transporters, and activating mitochondrial apoptosis. In addition to the natural presence of hepatotoxic components, contamination of dietary supplements and plant-based products by hepatotoxic compounds, such as metals, mycotoxins, pesticide, and herbicide residues, among others, can also occur<sup>(55,56)</sup>. Most of the studies included in our review did not evaluate the presence of contaminants which does not prevent us from discarding this hypothesis.

This study has some limitations that must be pointed out. It included only case report studies, with different criteria for HILI and DSILI. Also, many had incomplete data on the composition of the products used, the daily dose consumed, and the symptoms observed. We only included cases published in the scientific

literature, which does not fully reflect reality, as many cases of hepatotoxicity from dietary supplements and herbal products are not officially documented, also, those documented tend to be the most serious ones. The results of this work can be useful to warn about the potential risks of hepatotoxicity of dietary supplements and herbal products. The research was comprehensive, including cases of hepatotoxicity from different parts of the world and any period, providing an expanded overview of the topic. More studies need to be carried out to identify potential hepatotoxic substances in plants and food supplements, to identify groups and populations at risk, and to identify the real incidence of DILI / HILI in different locations around the world.

## CONCLUSION

Several cases of liver injury induced by dietary supplements and herbal products were identified, with numerous products involved, but among them, Herbalife<sup>®</sup>, OxyElite Pro<sup>®</sup>, Hydroxycut<sup>®</sup> products, and *Polygonum Multiflorum* herbs, green tea, and kava, were the most frequent. Most cases were in middle-aged women and adults, with a predominance of hepatocellular lesions. Herbal products were used by older individuals, associated with lower latency, and both hepatocellular and cholestatic injuries compared to dietary supplements. However, further studies are needed to better clarify the links and mechanisms between which each product causes liver damage. So far, this study demonstrates that the indiscriminate use of dietary supplements and herbal products was related to an alarming number of cases of liver injury, many of which have led users to liver transplantation or even death. Thus, increasing surveillance and regulation of these products is necessary to alert the population regarding the indiscriminate use of dietary supplements and herbal medicines.

## Authors' contribution

Assis MH: study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, drafting of the manuscript; Alves BC: study concept and design; technical support, analysis and interpretation of data, drafting of the manuscript; Luft VC: statistical analysis; technical support; critical revision of the manuscript for important intellectual content; Dall'Alba V: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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Assis MH, Alves BC, Luft VC, Dall'Alba V. Lesão hepática induzida por ervas e suplementos alimentares: uma análise agrupada de estudos de caso. *Arq Gastroenterol.* 2022;59(4):522-30.

**RESUMO – Contexto** – O consumo de ervas medicinais e suplementos alimentares é muito popular no mundo. Contudo, esses produtos não são inócuos e sua ingestão pode causar danos à saúde, especialmente dano hepático. **Objetivo** – Descrever os casos clínicos de lesão hepática induzida por ervas e suplementos alimentares, identificando os principais produtos envolvidos e as manifestações relacionadas a eles. **Métodos** – A busca na literatura foi realizada na base de dados PubMed, EMBASE, Google Escolar e LILACS usando as seguintes palavras-chaves: “*Chemical and Drug-Induced Liver Injury*”, “*Dietary Supplements*”, e “*Herbal*”, incluindo seus sinônimos. **Resultados** – Foram incluídos 189 artigos no estudo, totalizando 428 casos clínicos de lesão hepática induzida por drogas. Os agentes de lesão hepática mais frequentes foram produtos Herbalife, associados a 50 casos, Polygonum Multiflorum, a 25 casos, produtos Hydroxycut e chá verde, ambos associados a 19 casos, e produtos Hydroxycut e chá verde, associados a 16 casos. A maioria dos indivíduos necessitou de hospitalização (82,6%) e um número importante de casos evoluiu para óbito (3,6%), transplante hepático (8,9%) ou doença hepática crônica (1,9%). **Conclusão** – O uso indiscriminado de suplementos alimentares e ervas foi associado com um número alarmante de casos de lesão hepática. Os mecanismos pelos quais cada um dos produtos causa danos ao fígado ainda precisam ser melhor compreendidos, mas esta revisão é um alerta sobre o risco associado ao uso de produtos considerados inofensivos por grande parte da população.

**Palavras-chave** – Lesão hepática induzida por drogas; hepatotoxicidade; suplementos dietéticos; interações erva-droga.

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