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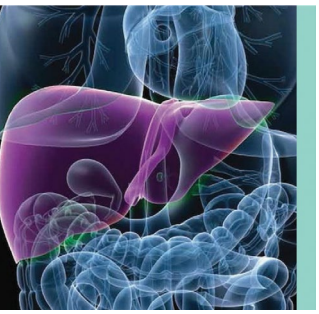

Impact of Herbal and Dietary Supplements Causing Drug-Induced Liver Injury in Latin America

Vinicius Nunes, and Nahum Mendez-Sanchez†*

Herbal remedies are therapeutic products and foods made from the leaves, seeds, flowers, and roots of plants, or from extracts thereof. The term HDS (herbal and dietary supplement) encompasses a broad spectrum of products, including—aside from herbs and herbal preparations—food supplements, vitamins, and minerals, some of which have been associated with liver injury.[1]

The Traditional Medicine Division of the World Health Organization recognizes that centuries-old used medicinal plants are important as therapeutic resources, but for herbal remedies to become products to use in public health systems, there should be evidence of safety and efficacy.[2]

However, more than 120 HDSs implicated in liver toxicity have been reported to date,[3] with an increase in the number of cases of HDS hepatotoxicity from 7% to 20% of the total cases of drug-induced liver injury (DILI) from 2004 to 2013.[4] Marketing regulations for HDS medicines are less strict than those for conventional drugs, leading to an abundance of easily accessible herbal medicine products.[5]

In 2016 in Latin America (LA), it was estimated that this market moved $22 billion, with an expectation of more than doubling its growth to $47 billion by 2025.[6]

DEFINITION AND DIAGNOSIS OF HERBAL-INDUCED LIVER INJURY

Hepatotoxicity by herbs or drugs is defined as an elevation of ALT (alanine aminotransferase) more than five times the upper limit of normality (ULN) or alkaline phosphatase more than two times. In the presence of symptoms or associated bilirubin elevation, a value greater than three times the ULN of ALT should already be considered.[7]

Abbreviations: ALT, alanine aminotransferase; DILI, drug-induced liver injury; HDS, herbal and dietary supplement; HILI, herbal-induced liver injury; LA, Latin America; LATINDILIN, Latin American DILI Network; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normality.

From the *Hospital Universitario Prof. Edgard Santos, Salvador de Bahia, Brazil; and †Liver Research Unit, Fundación Clínica Médica Sur, Mexico City, Mexico.

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A chronology between the use of the suspected substance and compatible liver damage is required, in addition to the exclusion of alternative causes. These elements can be quantified through a scale (Roussel Uclaf Causality Assessment Method [RUCAM]) that can be applied as a diagnostic tool[8] (Fig. 1).

A major limitation to standardizing the clinical pattern of liver injury caused by HDS products is the complexity of many of these plant-derived mixtures, which may contain multiple and even undeclared ingredients. Variations in preparations and dosages, or even in the product composition, make it difficult to ascertain the culprit ingredient. Indeed, in many HDS products, neither the composition nor the active ingredient is clearly identified.[9]

The main biochemical structures implicated in liver damage are alkaloids (especially pyrrolizidine) and terpenes, and HDSs that contain these compounds should be carefully evaluated. Others with significant hepatotoxic potential are anthraquinones and catechins, although sometimes they even appear as hepatoprotectants.[10] Genetic susceptibility is also important,[11] which soon may be used to guide or contraindicate the use of therapies.

The LiverTox database can be consulted about risk for hepatotoxicity and pattern of damage for numerous drugs, but it contains information about few HDSs (i.e., just more than 60 substances).[12]

EPIDEMIOLOGY

Consumption of HDSs varies among countries. In Mexico, which has the second largest diversity of medicinal plants (behind China) with 4500 species, it is estimated that 90% of the population uses them, a pattern of consumption similar to Eastern countries. In the United States, this number is approximately 50%, for example.[4,13]

The LA population is marked by the strong indigenous influence and migration of African slaves, who have benefited from the medicinal use of herbs through millenary knowledge. The religious leaders of these ethnic groups also continue to assume the role of health agents.[5]

But the pattern of consumption has been changing rapidly, and in recent decades a huge market has opened for people seeking herbs for a "natural" and harmless way to promote weight loss and well-being.[14] Parallel to the increase in HDS use is a growing economic market and a profitable industry. Although acknowledging the difficulties in calculating sales data derived from the use of herbs worldwide, the forecast was to reach $107 billion in 2017, representing an 12% increase per year, higher than that for conventional drugs, which has been expected to increase about 5% annually.[1]

LA countries represented around 8% of the global supplement industry market. However, this region shows one of the highest growth rates, at 9% in 2017, and in

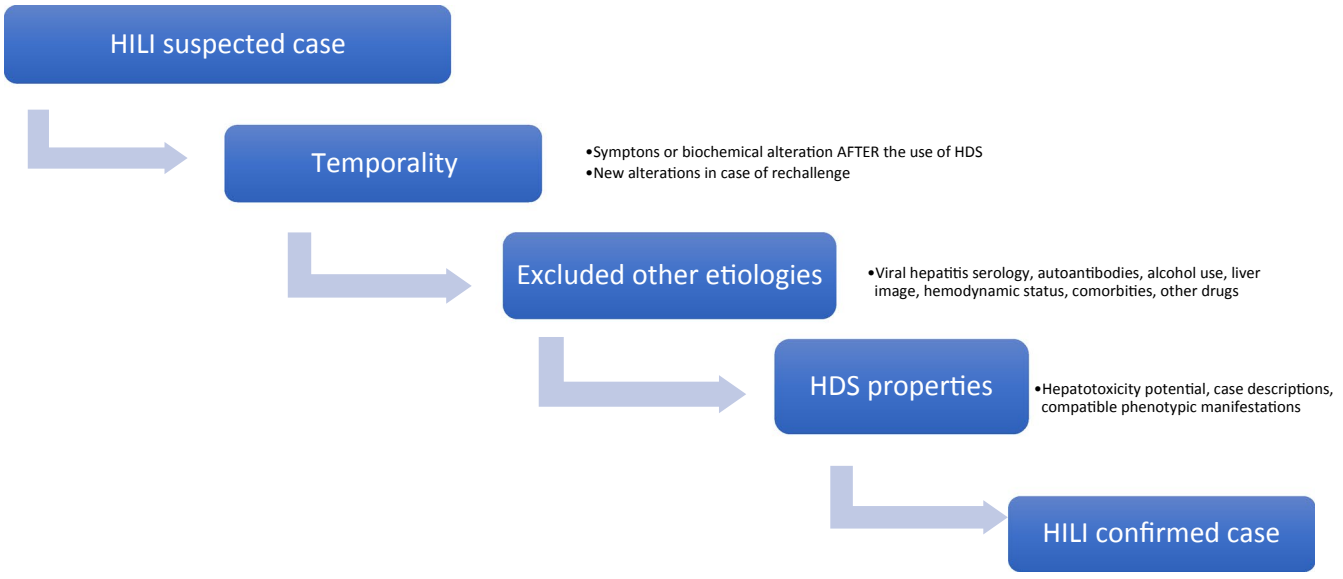

FIG 1 HILI diagnosis algorithm.

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particular herbs and botanicals achieved 11% growth the same year.[1]

Due to regional particularities, a productive network was established between hepatologists from various LA countries (Latin American DILI Network [LATINDILIN]) and recently catalogued a total of 311 cases of DILI, 37 of them due to HDS, with the distribution listed in Table 1.[14] It showed that 10% of the acute liver injury cases were attributed to HDS products. The incidence may be low, but most herbal-induced liver injury (HILI) cases are not reported.[9]

A recent review grouped all reported cases ever published in LA countries, totaling 17 patients personal communication, submission to publication. Asian Centella was the most commonly reported herb (33%) among the single-ingredient products, and the Herbalife cases were the most commonly reported (63%) as multi-ingredient products.[15,16] In such cases, RUCAM cannot discriminate between the agents, and the case has to be finally ascribed to the combination of products.[17] Some herbs species identified in this analysis, such as *Argemone mexicana L.* and *Cochlospermum vitifolium*, were endemic to LA.[18] Besides this, *Aloe vera*, *Camellia sinensis*, and *Centella asiatica* species are being used in several LA countries included in the composition of phytotherapies and manufactured food supplements, and they are well-known hepatotoxins. The other cases analyzed in the current series were related to Euforia, Shen Min, and Tiodrix HR herbal supplements.[19] The composition of these products had some herbs in common, such as green tea, *Morinda citrifolia* (Noni), *Polygonum multiflorum*, *Cimicifuga racemosa*, Black cohosh, Ginkgo biloba, and thioctic acid. In relation to severity, nine (53%) cases required hospitalization, and one patient (6%) experienced acute liver failure and died (personal communication, submission to publication).

TABLE 1. HILI CASES IN LATINDILI REGISTRY

HDS	Frequency	Indication
Anabolic steroids	14	Muscle hypertrophy
Herbalife products	5	Variable
Garcinia cambogia	3	Weight loss
Lipodex	2	Weight loss
Centella asiatica	2	Variable
Camellia sinensis	2	Weight loss
Echinacea	1	Anti-infectious
Monascus purpureus	1	Hyperlipemia
Hydroxycut	1	Weight loss
Ginkgo biloba	1	Memory
Peumus boldus	1	Gastrointestinal disorder
Equisetum arvense	1	Variable
Chitosan	1	Variable
Kombucha tea	1	Variable
Pelargonium sidoides	1	Anti-infectious

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Of the herbs highlighted as frequently (>10 cases) causing HILI in a predominantly Asian systematic review with 334 cases identified the causative herbs, there were no agents coincident with the cases described in LA.[20] In comparison with the Spanish Registry, LA HILI cases were more represented.

Another interesting finding was that almost half of all hepatotoxicity cases by drugs used some associated HDSs. In the Brazilian population of predominantly low-income individuals and those without access to regular medical care, the most frequent use was of herbs infusions (teas and drunks), whereas individuals who attended private clinical offices, with greater economic and cultural power, the consumption was predominantly industrialized supplements, which is compatible with North American data.[21]

The various cases described in LA have similar characteristics to those of DILI, and in agreement with the other international cohorts, most of them were female, with an average age around 50 years and with a hepatocellular phenotypic profile, sometimes varying in severity, giving the impression that HDS cases are more severe.[4,20]

It is necessary to consider that consumers of HDSs in most cases are not evaluated at medical appointments and with laboratory tests as often as those who use allopathy, and perhaps that is why the cases who seek medical attention are the most severe, already with symptoms, notably jaundice.

CONCLUSIONS

HDS consumption increases exponentially and, consequently, so does the number of hepatotoxicity cases associated with its consumption. LA has abundant biodiversity and is culturally prone to the use of herbs. Therefore, for the rational and safe use of HDSs, we need to deepen our knowledge of regional epidemiology and the substances with the highest potential for harm.

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CORRESPONDENCE

Vinicius Santos Nunes, Hospital Universitario Prof. Edgard Santos, Gastroenterology and Hepatology Department, Augusto Viana st s/n, Canela, Salvador de Bahia, Brazil. PO Box: 40.110-060, Tel: + 55 71 32838395. E-mail: snunesvinicius02@gmail.com

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