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TITLE: The Contents of Herbal and Dietary Supplements implicated in liver injury in the United States are frequently mislabeled

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Background

Herbal and dietary supplements (HDS) are being increasingly used for touted "health benefits" (1) and are responsible for over $36B in commerce in the US each year. (2,3) Broadly stated, HDS comprise single and multi-ingredient products that may include herbals, vitamins/minerals and amino acids. Hepatotoxicity from HDS is increasingly being recognized. (4) In the US Drug Induced Liver Injury Network(DILIN) prospective study, products used as appearance and performance enhancing (APE) supplements are the most common subclass of HDS leading to liver injury. Patients with hepatotoxicity from weight loss and other non-APE products can also sustain severe liver injury. Despite these potential risks, HDS remain widely available in retail outlets and on the internet with little to no required safety or efficacy testing. As a result, consumers are exposed to compounds whose biological effects are largely unknown in humans. In addition, unlabeled ingredients added intentionally, accidentally, or as a byproduct of the manufacturing process comprise yet another risk of HDS to the consumer. The HDS collected from DILIN enrollees were used to verify product labels and thus estimate the rate of label

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inaccuracy, as well as to search for known hepatotoxins and pharmaceuticals among HDS implicated in causing liver injury.

Objective:

The purpose of this study was to determine the veracity of the label on HDS consumed by patients enrolled into the DILIN, and to identify potential hepatotoxins in these products.

Methods:

The DILIN, a multicenter consortium funded by the National Institute for Diabetes and Digestive and Kidney Diseases, is studying the etiologies, risk factors, and outcomes of patients with drug induced liver injury (DILI). All DILIN cases undergo a causality adjudication process that determines the likelihood of liver injury due to a drug or dietary supplement and implicates the product (drug or HDS) responsible.

Between 2003 and 2015, the DILIN prospective study enrolled 341 HDS from 1268 patients with suspected DILI; 272 of these products had labels listing their ingredients and these underwent chemical analysis at the National Center for Natural Products Research of the University of Mississippi using ultra-high-performance liquid chromatography coupled to a quadrupole time-of-flight mass spectrometry (UHPLC-QToF-MS). Of the 272, 96 products were directly implicated as a cause for liver injury in 71 patients.

The HDS products also were analyzed for known hepatotoxins, including aflatoxins, anabolic steroids, anthraquinones, pyrrolizidine alkaloids; and pharmaceuticals. HDS were grouped per their marketed purpose for use, such as for APE or weight loss. Mislabeling was defined as when the chemical analysis could not verify all ingredients listed on the label.

Findings:

Of the 272 products tested, only 132 had labels that accurately reflected the compounds identified by chemical analysis and thus 140 (51%)were mislabeled. These 140 products lacked at least one of the listed compounds (number of ingredients ranged from 1 to 21), and 55 products contained compounds not listed on the label, including 2 that were pharmaceuticals. The overall mislabeling rate was 51% and rates were higher for steroidal (82%) than botanical (44%) and vitamin (49%) products. When categorized by marketed purpose of the HDS, the rates of mislabeling were highest for sexual enhancers, APE, and weight loss products (Table). Adulterants found in the 91 products with known hepatotoxins included anabolic steroids in 13 of 26 products; diclofenac in an agent for arthritis; and

tamoxifen in a bodybuilding product. In the two latter cases, the clinical features of liver injury were consistent with the adulterants' reported biochemical and clinical liver injury pattern.

Discussion:

We identified an alarmingly high rate of mislabeling in HDS collected from patients enrolled into the DILIN study. Products used for APE and weight loss had the highest rates of mislabeling. In the two cases of pharmaceutical adulteration, the clinical features were highly consistent with that reported due to the identified adulterants. (5)

Our findings highlight that a large proportion of commercially available HDS are mislabeled, exposing consumers to substances unknowingly, some of which may be responsible for liver injury. At this time, we are unable to determine which of the compounds or combination of compounds are responsible for the observed liver injury. Nonetheless, the high rate of mislabeling including identification of agents recognized to cause liver injury may expose consumers to unrecognized risk including interactions with prescribed medications. These preliminary findings suggest that more stringent regulation of HDS is required to improve the accuracy and to verify product labels to avoid potential adverse health events including liver injury.

References:

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Table: Mislabeling in HDS collected by the DILIN

Category	HDS with Labels	Mislabeled HDS (%)
General Health	53	26 (49%)
Appearance & Performance Enhancing	46	37 (80%)
Weight Loss	36	26 (72%)
GI Symptoms	22	9 (41%)
Energy Boosters	5	3 (60%)
Sexual Enhancers	4	4 (100%)
Misc or Unknown	106	35 (33%)
TOTAL	272	140 (51%)