# Accepted Manuscript


Herbal Dietary Supplement Associated Hepatotoxicity: An Upcoming Workshop and Need for Research

Raj Vuppalanchi, Victor Navarro, Maricruz Vega, Herbert L. Bonkovsky, Leonard Seeff, Jose Serrano

PII: S0016-5085(15)00022-0
DOI: 10.1053/j.gastro.2015.01.004
Reference: YGAST 59540

To appear in: *Gastroenterology*

Please cite this article as: Vuppalanchi R, Navarro V, Vega M, Bonkovsky HL, Seeff L, Serrano J, Drug-Induced Liver Injury Network (DILIN), Herbal Dietary Supplement Associated Hepatotoxicity: An Upcoming Workshop and Need for Research, *Gastroenterology* (2015), doi: 10.1053/j.gastro.2015.01.004.

# Herbal Dietary Supplement Associated Hepatotoxicity: An Upcoming Workshop and Need for Research

Raj Vuppalanchi[1], Victor Navarro[2], Maricruz Vega[2], Herbert L. Bonkovsky[3], Leonard Seeff[2], Jose Serrano[4]; Drug-Induced Liver Injury Network (**DILIN**).

[1]Division of Gastroenterology & Hepatology, Indiana University, Indianapolis, IN
[2]Division of Hepatology, Einstein Medical Center, Philadelphia, PA
[3] Department of Internal Medicine, Sections on Gastroenterology and Molecular Medicine and Translational Science, Wake Forest University School of Medicine, Winston-Salem, NC
[4]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD

**Corresponding Author:**
Victor Navarro, MD
Division of Hepatology
Einstein Medical Center
5501 Old York Road, 505 Klein
Philadelphia, PA 19141
P: (215) 456-5967
F: (215) 456-8058
E: navarrov@einstein.edu

**Short title:** DILIN Herbal and Dietary Supplement Research

**Word Count:** 958 1256

**Grant Support**

The DILIN network is supported by the National Institute of Diabetes and Digestive and Kidney Diseases under the following cooperative agreements: 1U01DK065021, 1U01DK065193, 1U01DK065201, 1U01DK065193, 1U01DK065184, 1U01DK065211, 1U01DK065238 and 1U01DK065176.

Use of herbal dietary supplements (HDS) in the U.S. is increasing as evidenced by consumer spending that has increased annually between 1999 and 2010, with the exception of 2002 and 2003. Indeed, the amount spent on HDS in 1999 was 4 billion dollars, increasing to 5 billion dollars in 2010 and 5.6 billion dollars in 2012.[1-4] Their actual safety and benefit, however, are questionable.[5,6] Conventional drugs are required to undergo careful clinical trials and receive approval from the Food and Drug Administration (FDA) before being marketed in the US. In contrast, under the Dietary Supplement Health and Education Act of 1994 (DSHEA), manufacturers of dietary supplements are themselves responsible for ensuring the safety of their products before they are released to the market (http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148003.htm). Scientific evidence that the products are safe and effective is required only when there is a claim for cure or for prevention of human disease.

The potential for HDS to cause hepatotoxicity is confirmed by a recent report from the Drug Induced Liver Injury Network (DILIN) demonstrating that many types of HDS, particularly those used for bodybuilding, have the capacity for causing liver injury.[5] The DILIN is a multicenter research network in the U.S. developed to study patients with hepatotoxicity due to conventional medications and HDS. Approximately 15% of drug induced liver injury cases ascertained by the DILIN are attributable to HDS, and there now are more than 130 cases of liver injury related to HDS in the DILIN database. The DILIN experience showed that HDS used for non-bodybuilding purposes (e.g., weight loss) are associated with more severe liver injury than is the injury resulting from prescription medications. This is apparent from the finding that 13% of study participants suffering from hepatotoxicity due to non-bodybuilding HDS required transplantation as compared to only 3% of those with conventional medication associated liver injury ($P< 0.001$).[5] Importantly, the DILIN was not designed as a population-based study, so that the true incidence of liver injury in the U.S. due to herbal products is yet to be established This

notwithstanding, the DILIN's findings are particularly important against the backdrop of the current regulatory environment for HDS, which neither promotes nor mandates research on their safety or efficacy. A survey of the literature indicates that HDS-related hepatotoxicity is indeed a world-wide problem. Data from a Spanish Liver Toxicity Registry showed that HDS products accounted for 2% of all cases of identified liver injury between 1994 and 2006 and that they ranked as the 10$^{th}$ most common therapeutic group.[7] Because of the wide use of HDS in China, India, other countries in Southeast Asia as well as Africa and Central America, the incidence in these countries could be much higher than it is in western countries. This likelihood is supported by prospective studies from Korea and Singapore that reported HDS as being responsible for 73% and 71%, respectively, of all their identified cases of hepatotoxicity.[8, 9]

The widespread use of HDS, the permissive U.S. regulatory environment for dietary supplements, and the potential toxicity attributable to HDS give context to the need for research in this area. Little systematic investigation has been performed and an understanding of the hepatotoxic potential of HDS is limited to observational studies. Moreover, protection of the public from potentially injurious effects of HDS depends upon the FDA's ability to identify harmful products or ingredients after release to the market, and their recommendation that they then be removed from use.

The approach to studying toxicity attributable to HDS is confounded by many factors. First, HDS may consist of multiple ingredients in concentrations that may vary from batch to batch. Second, multiple HDS products may be used and often combined with conventional medications, raising the possibility of interactions. Third, some HDS may cause liver injury indirectly because of chemical [10] or microbial contamination and adulteration.[11]. More recent regulation aims to standardize current good manufacturing practices for HDS (http://www.fda.gov/NewsEvents/Newsroom/Press Announcements/2007/ucm108938.htm). These factors, ostensibly barriers to research, give some direction for future studies to evaluate hepatotoxicity due to HDS.

The DILIN aims to better understand hepatotoxicity associated with HDS. As its first endeavor, it established a repository for HDS that have been linked to hepatotoxicity. Many that were implicated in liver injury have been retrieved from patients and are available for study by contacting the Chairman of the DILIN HDS Subcommittee (VN, corresponding author). As of October 1, 2014, 318 HDS products comprise this repository, collected from 119 patients, enrolled at 10 DILIN clinical sites. Already, the repository has proven itself to be an important resource for exploring the hepatotoxic potential of certain ingredients. For example, in a detailed product analysis involving green tea extracts, about 40% of products found to contain green extracts did not identify its presence on the label[12]. However, no relationship was found between the concentration of green tea extract and the severity of liver injury, suggesting either that idiosyncrasy accounted for the injury or that another ingredient was responsible.[12]. Collaboration with scientists interested in the chemical composition of botanical products will add future value to this repository by providing the means to seek the injurious ingredients. Arguably, the greatest challenge in studying hepatotoxicity associated with HDS lies in the complexity of the products, making difficult the identification of the precise ingredient or combination of ingredients responsible for the injury. The confident identification of a toxic culprit will require labor intensive chemical dissection of HDS into their component parts and testing each individual and combination of ingredients for potential toxicity. This task will, however, be formidable for even the most well-funded and resourceful laboratories.

The lack of a conventional classification scheme or nomenclature for HDS complicates scientific investigation, because commercial HDS products may contain multiple constituents and combinations of ingredients. Thus, the DILIN has developed a nomenclature for HDS based upon their primary purported marketed benefit. A structured classification for HDS will allow comparison of liver injury cases attributed to the same or similar products and identify characteristic clinical patterns of injury, unique to a given type of product or ingredient. This

schema is founded upon the frequency with which products were implicated by the DILIN (Table 1).

Much is yet to be learned about behavioral factors that contribute to toxicity resulting from HDS. Patterns of use and overuse have not been studied and little is known of where consumers obtain information on use of products. The DILIN study offers the opportunity to expand knowledge about these features through the extensive clinical and behavioral data being collected.

Claims that HDS "stimulate", "maintain", "support", "regulate", "cleanse" or "promote" health will continue to entice consumers. However, given the now proven hepatotoxic potential of some types of products, it is the responsibility of health care providers and physician scientists to sound the alarm and to create a research agenda to mitigate liver injury. In response to this need, a joint Workshop on Liver Injury from Herbal and Dietary Supplements will be held on May 5-6, 2015 at the Lister Hill Auditorium on the campus of the National Institutes of Health, co-sponsored by the American Association for the Study of Liver Diseases (AASLD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The Office of Dietary Supplements, the FDA, the Center for Disease Control, and the U.S. Agriculture Department also will support the meeting. This workshop aims to bring together experts from the broad range of disciplines involved in the evaluation of HDS and define opportunities and promising directions for future research. More information about the Workshop and Fellowship Travel Awards can be found at http://www.niddk.nih.gov/news/events-calendar/Pages/Liver-Injury-Herbals-Dietary-Supplements.aspx#tab-event-details.

**Acknowledgements**

We thank research participants for enrolling in the DILIN studies and research coordinators for their dedication and contributions to the DILIN.

Dr. Raj Vuppalanchi has served on the Gilead and Genentech Speaker's bureau.

Dr. Victor Navarro has received support for research studies from The National Institutes of Health.

During the past three years, Dr. Bonkovsky served as a paid advisor to Alnylam, Clinuvel, Inc., and Rockwell Scientific. He has received support for research studies from The National Institutes of Health, The American Porphyria Foundation, Alnylam, Clinuvel, Novartis and Vertex.

Ms. Maricruz Vega has no conflicts of interest.

Dr. Leonard Seeff has no conflicts of interest.

Dr. Jose Serrano has no conflicts of interest.

**TABLE 1. The DILIN HDS classification scheme based on the primary marketed purpose/use (mutually exclusive categories) and inventory in the HDS repository.**

| | ***DILIN HDS Category*** | ***# of Products*** | ***% of Products*** |
|---|---|---|---|
| *1* | General health/Well being | 71 | 22.3 |
| *2* | Bodybuilding | 48 | 15.1 |
| *3* | Weight loss | 40 | 12.6 |
| *4* | Gastrointestinal symptoms | 25 | 7.9 |
| *5* | Immune support | 13 | 4.1 |
| *6* | Joint support/arthritis | 9 | 2.8 |
| *7* | Toxin removal | 8 | 2.6 |
| *8* | Energy booster | 8 | 2.5 |
| *9* | Sexual performance | 3 | 0.9 |
| *10* | Depression/anxiety | 3 | 0.9 |
| *11* | Pain relief | 2 | 0.6 |
| *12* | Sedative/hypnotic | 1 | 0.3 |
| *13* | Miscellaneous | 87 | 27.4 |
| | *TOTAL* | 318 | 100 |

**References:**


1. Lindstrom A OC, Lynch ME, Blumenthal M. . Herb supplement sales increase 5.5% in 2012: herbal supplement sales rise for 9th consecutive year; turmeric sales jump 40% in natural channel. . HerbalGram 2013:60-65.
2. Timbo BB, Ross MP, McCarthy PV, et al. Dietary supplements in a national survey: Prevalence of use and reports of adverse events. J Am Diet Assoc 2006;106:1966-74.
3. Barnes PM, Powell-Griner E, McFann K, et al. Complementary and alternative medicine use among adults: United States, 2002. Adv Data 2004:1-19.
4. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 1998;280:1569-75.
5. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014;60;1399-1408.
6. Seeff LB, Bonkovsky H, Navarro VJ, Wang G. Herbals and the Liver - A Review of Adverse Effects and Mechanisms. Gastroenterology 2014;in press.
7. Garcia-Cortes M, Borraz Y, Lucena MI, et al. [Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry]. Rev Esp Enferm Dig 2008;100:688-95.
8. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol 2012;107:1380-7.
9. Wai CT, Tan BH, Chan CL, et al. Drug-induced liver injury at an Asian center: a prospective study. Liver Int 2007;27:465-74.

10. Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA : the journal of the American Medical Association 2008;300:915-23.
11. Stickel F, Droz S, Patsenker E, et al. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with Bacillus subtilis. J Hepatol 2009;50:111-7.
12. Navarro VJ, Bonkovsky HL, Hwang SI, et al. Catechins in dietary supplements and hepatotoxicity. Dig Dis Sci 2013;58:2682-90.