Review Article **OJGH (2022) 5:62**

Open Journal of Gastroenterology and Hepatology
(ISSN:2637-4986)

Trends in Herbal and Dietary Supplement Use Among U. S. Adults with Chronic Liver Disease

Khan A[a,b]*, Mitsuhashi, S[a], Chauhan K[a], Mujumdar S[a], Erwin R[a], Zheng M[a], Yalamanchili S[a], Reddy S[a], Navarro V[c], Halegoua-DeMarzio D[a,b]*

[a] Thomas Jefferson University Hospital, Department of Medicine, Philadelphia, PA, USA
[b] Thomas Jefferson University, Department of Medicine, Division of Gastroenterology & Hepatology, Philadelphia, PA, USA
[c] Einstein Medical Center, Department of Medicine, Division of Gastroenterology & Hepatology, Philadelphia, PA, USA

ABSTRACT

Herbal and dietary supplements (HDS) are used by over 50% of Americans, but commonly their use is not reported to healthcare providers. The aim of this study is to determine the prevalence of HDS use among patients with Chronic Liver Disease (CLD), with a focus on those using supplements known to cause hepatotoxicity. We accessed 61,951 individuals polled in the NHANES database between 2001-2011, which represented a population size of 1,763,482,931. 573 respondents reported a history of CLD (population size of 19,998,331.655). Of those 573 respondents, 41 respondents (population size 1,399,884) endorsed using HDS that are associated with causing hepatotoxicity, which are listed under the NIH complied master list. Our study demonstrates the need for better counseling of patients on the potential risks of these readily available products.

Keywords: Herbal supplements; dietary supplements; Chronic liver disease; End stage liver disease; hepatotoxicity; Herbalife; Hydroxycut; Drug induced liver injury

Declaration of conflict of interest: The authors declare no conflict of interest.

***Correspondence to Author:**
Dina Halegoua-DeMarzio
Department of Gastroenterology and Hepatology Thomas Jefferson University, 132 South 10th Street, Main Building, Suite 480, Philadelphia, PA 19107,

How to cite this article:
Khan A, Mitsuhashi, S, Chauhan K, Mujumdar S, Erwin R, Zheng M, Yalamanchili S, Reddy S, Navarro V, Halegoua-DeMarzio D. Trends in Herbal and Dietary Supplement Use Among U. S. Adults with Chronic Liver Disease. Open Journal of Gastroenterology and Hepatology, 2022, 5:62.

eSciPub LLC, Houston, TX USA. Website: https://escipub.com/

1. Introduction

Over the last two decades, incidence of acute liver injury due to herbal and dietary supplements (HDS) has increased [1, 2]. The National Center for Complementary and Integrative Health defines dietary supplements as herbs, vitamins, and probiotics. According to the CDC (Centers for Disease Control), in 2017–2018, 57.6% of adults aged 20 and over reported using HDS in the past 30 days, with trends showing use of HDS products increased with age as did the use of multiple HDS products at one time. One-quarter of adults aged 60 or older reported taking four or more dietary supplements, and 80.2% within this age range were women. From 2007–2008 to 2017–2018, dietary supplement use increased in all age groups among U.S. (United States) adults [3].

HDS are consumed for a variety of purposes including weight loss, bodybuilding, immune support, or general wellbeing. Despite these claims and widespread public approval, HDS are not FDA approved or at times even regulated [4]. A new bill was introduced in 1994 titled the Dietary Supplement Health and Education Act [5]. It defined a dietary supplement as a vitamin, mineral, herb or other botanical, amino acid, or dietary substance to supplement the diet that may exist as a concentrate, metabolite, constituent, extract, or combination of ingredients. The Act permitted manufacturers to market such products without registering them or requiring FDA approval. Manufacturers of herbal products were now responsible for ensuring the safety of their supplements and their ingredients. Whereas the FDA requires pharmaceutical companies to prove that their drugs are effective and safe before marketing, dietary supplements could now be marketed without these requirements, shifting the burden to the FDA to prove lack of safety [6, 7].

The Drug-Induced Liver Injury Network (DILIN) studied hepatotoxicity caused by conventional medications and HDS. To characterize hepatotoxicity and its outcomes from HDS versus medications, patients with hepatotoxicity attributed to medications or HDS were enrolled prospectively between 2004 and 2013. The study took place among eight U.S. referral centers that are part of the DILIN. The study found that the proportion of liver injury cases attributed to HDS in DILIN had increased significantly. Liver injury from non-bodybuilding HDS is more severe than from bodybuilding HDS or medications, as evidenced by differences in unfavorable outcomes (death and transplantation) [8].

With the growing concerns of drug induced liver injury (DILI) and lack of well controlled trials on pharmacokinetics of HDS, there are concerns for worse outcomes in HDS induced toxicity in patients with a diagnosis of CLD. The aim of this study is to determine the prevalence of hepatotoxic HDS in the U.S. regarding their use among patients with CLD.

2. Materials and Methods

2.1. NHANES Database

The US National Health and Nutrition Examination Survey (NHANES) is a cross sectional survey of a nationally representative sample of the civilian, non-institutionalized U.S. population designed to monitor the nation's health and nutrition status. NHANES uses a complex multistage probability sampling design to select participants, and continuous data collection has been conducted in 2-year cycles [9]. All participants provide written informed consent before completing the NHANES, and there are no patient identifiers in the publicly available NHANES database.

According to module-3 of NHANES tutorial, NHANES is designed to sample larger numbers of certain subgroups of public health interest to increase the reliability and precision of estimates of health status indicators for these population subgroups. The sample weights are used to adjust the sample population based on race, Hispanic ethnicity, income, sex, and age. They are meant to compensate for differences in the subject selection or response rates at various stages of the survey. Thus, estimates from these

subgroups combined with national estimates reflect the true relative proportions of these groups in the U.S. population. The full methodology and data collection have been described previously and are available on the NHANES website [9].

2.2. The Questionnaires

Using the NHANES database from 2001 to 2012, we identified the survey population that provided self-reported personal interview data on a broad range of health conditions. The NHANES MCQ questionnaire section is modeled on the "Medical Conditions" questionnaire section of the U.S. National Health Interview Survey. We targeted the population that self-identified as having CLD, both males and females, aged ≥20 years. Participants who answered "yes" to the question, "Do you still have a liver condition" were defined as having CLD.

We then identified the total number of respondents that reported taking HDS by using the dietary questionnaire. We specifically used the "Dietary Supplement Use 30-Day" data set. The participants were asked "Have you used or taken any vitamins, minerals or other dietary supplements (prescription and non-prescription) in the past 30 days?" The name from the front of the product label was specifically asked and collected into the data. The following list was defined as HDS: Aloe Vera, Ashwagandha, Black Cohosh, Copper, Echinacea, Garcinia, Ginkgo Biloba, Ginseng, Glucosamine, Green Tea, Hydroxycut, Iron, Kava Kava, Manganese, Niacin, Pennyroyal oil, Red Yeast Rice, Saw Palmetto, Turmeric, Valerian Root, and Vitamin A.

2.3. LiverTox Database

After we extrapolated which supplements each respondent was taking, we cross referenced known HDS that are hepatotoxic with respondents who reported having CLD by using the LiverTox Database. The LiverTox compendium lists herbs or supplements having an A, B, C, or D rating, meaning a drug has "well known or more than 50 cases described," "known or highly likely or 12-50 cases described," "probable or less than 12 cases described," or possible hepatotoxin and only a rare cause of liver injury respectively, based on published reports.

2.4. Population Size

We accessed 61,951 individuals polled in the NHANES database, representing a population size of 1,763,482,931, of which 573 respondents reported a history of CLD (population size of 19,998,331.655). Of those 573 respondents, 41 respondents (population size 1,399,884) endorsed using HDS that are associated with causing hepatotoxicity, which are listed under the NIH complied master list.

2.5. Statistical Analysis

Demographic variables included age, gender, and race/ethnicity. Age was stratified by decades: 20-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years. Race and ethnicity were classified into the following classifications: Non-Hispanic White, Non-Hispanic Black, Hispanic (including Mexican American), and other races (including multi-racial). We then identified individuals with CLD and summarized their background characteristics. Demographic, clinical characteristics, and dietary supplements were reported as proportion or means. All estimated standard errors were calculated using sampling weights accounting for the complex survey design of NHANES. Taylor series linearization was used to calculate 95% Confidence Intervals (CIs) for the estimated occurrence. All statistical analyses were performed using STATA statistical software version 17.0 (College Station, TX, USA).

3. Results

Of the 61,951 (population size of 1,763,482,931) individuals polled in the NHANES data, 573 respondents (population size of 19,998,331.655) reported a history of CLD, while 445 respondents denied having a history of CLD. 60,933 participants did not answer the question. Of those respondents with a history of CLD, 56%

were males, 44% were females, and the average age was 54 years old. These demographic data are included in tables 1 and 2 below.

Of the 573 respondents who reported a history of CLD, 41 individuals (population size of 1,431,881) reported taking hepatotoxic HDS, while 532 did not. This, along with the frequencies of the use of specific hepatotoxic HDS, are shown in tables 3 and 4 below.

Of the 41 respondents that admitted taking known hepatotoxic HDS, 56% were males, and 44% were females. The distributions of specifically hepatotoxic HDS by sex, age in decades, and race/ethnicity are demonstrated in tables 5, 6, and 7 below.

Table 1. Proportions of NHANES survey respondents with CLD

Has chronic liver disease	Frequency	Percent	Cumulative
No	445	0.72	0.72
Yes	573	0.92	1.64
Not recorded	60933	98.36	100.00
Total	61951	100.00	

Table 2. Sex distribution of respondents with CLD

Gender	Frequency	Percent	Cumulative
Male	321	56.02	56.02
Female	252	43.98	100.00
Total	573	100.00	

Table 3. Distribution of patients with CLD by use of HDS

Taking HDS?	Frequency	Percent	Cumulative
No	532	92.84	92.84
Yes	41	7.16	100.00
Total	573	100.00	

Table 4. frequency and proportions of hepatotoxic HDS that were used by survey respondents

HDS Type	Frequency	Percent	Cumulative
Aloe Vera Alone	2	4.88	4.88
Glucosamine alone	7	17.07	21.95
Green Tea alone	2	4.88	26.83
Hydroxycut alone	1	2.44	29.27
Iron alone	16	39.02	68.29
Niacin alone	1	2.44	70.73
Red Yeast Rice alone	1	2.44	73.17
Saw Palmetto alone	1	2.44	75.61
Vitamin A alone	2	4.88	80.49
2 types of HDS*	7	17.07	97.56
3 or more types of HDS*	1	2.44	100.00
Total	41	100.00	

*Supplements that were in combination were glucosamine, valerian Root, Saw palmetto, Niacin, Iron, Turmeric, Aloe vera, green tea, Ginko Bilboa and Iron.

Table 5. Sex distribution of patients taking known hepatotoxic HDS

Gender	Frequency	Percent	Cumulative
Male	18	43.90	43.90
Female	23	56.10	100.00
Total	41	100.00	

Table 6. Age distribution of patients taking known hepatotoxic HDS

Age in decades	Frequency	Percent	Cumulative
20-29	2	4.88	4.88
30-39	3	7.32	12.20
40-49	9	21.95	34.15
50-59	11	26.83	60.98
60-69	10	24.39	85.37
70+	6	14.63	100.00
Total	41	100.00	

Table 7. Race/Ethnicity distribution of patients taking known hepatotoxic HDS

Race/ethnicity	Frequency	Percent	Cumulative
White	22	53.66	53.66
Black	3	7.32	60.98
Hispanic	12	29.27	90.24
Other	4	9.76	100.00
Total	41	100.00	

4. Discussion

The Dietary Supplement Health and Education Act of 1994 established a regulatory framework for manufacturing and marketing HDS [7]. The Act, however, remains under much scrutiny, as many do not feel it grants the FDA enough power to properly protect consumers from potentially unsafe HDS. For instance, manufacturers are still not required to submit any pre-market safety information regarding their products. The products are not required to be proven safe nor effective prior to becoming available to consumers. Instead, the FDA relies on adverse event reporting to monitor supplements after they have been made available to the public.

These issues with the regulation of HDS provide an important opportunity for healthcare providers (HCP) to counsel their patients regarding the safety of any supplements they may be taking. With the growing number of HDS becoming available to patients, it is more important than ever for HCP to obtain thorough histories from their patients, including any over-the-counter supplements. By staying informed regarding HDS and providing education to patients, HCP can play a crucial role in preventing dangerous side effects.

The extent of hepatic injury from HDS ranges from asymptomatic elevation in liver tests to acute liver failure causing death or requiring liver transplantation [11]. Certain products can interfere with CYP450 activity, while other products cause damage to the hepatic sinusoidal cells. Bodybuilding HDS tend to cause a cholestatic liver injury pattern with a better prognosis and improvement without the need for a liver transplant, while non-bodybuilding HDS cause a more hepatocellular type of liver injury; however, there is significant variation between patients [1, 2, 10].

With the growing popularity of HDS, there has been a concomitant rise in the incidence of HDS-induced liver injury [11]. A safe herbal product may be contaminated by toxic compounds

leading to hepatotoxicity. There have been cases of contamination of heavy metals, pesticides, herbicides, microorganisms, and classical pharmaceutical products, as was seen with curcuma longa (turmeric) [12]. This includes Nimesulide, a non-steroidal anti-inflammatory medication with a rare side effect of severe hepatotoxicity resulting in fulminant liver failure still used in several countries [12].

A recent study examined patients diagnosed with drug induced acute liver failure (DIALF) on the transplant waitlist in the United Network for Organ Sharing (UNOS) database between 1995 and 2020 and found that there had been an eight-fold increase in HDS-related liver failure necessitating waitlisting for liver transplantation in the U.S. during those 25 years [11]. Furthermore, in one study, the need for liver transplantation was higher in patients with liver injury due to HDS products compared to DILI caused by conventional drugs [12, 13].

Our study highlighted the concerns of category A, B, C, and D supplements. In our dataset, 41 patients (population size of 1,431,881) with CLD reported using potentially hepatotoxic HDS including saw palmetto, green tea extract (GTE), Hydroxycut, Herbalife, or glucosamine. We found that 7 respondents (population size 17,709) were taking a combination of hepatotoxic HDS described in table 4. This finding supports the possibility that patients with CLD were either not paying close attention to avoiding HDS with possible hepatotoxic side effects or not discussing these supplements with their HCP.

Nonetheless, there are not enough controlled randomized studies on how HDS affect individuals with CLD. Results from our study showed that 41 of 573 respondents reported using HDS products associated with hepatotoxicity while having a history of CLD. It has been previously noted that patients with non-alcoholic fatty liver disease (NAFLD), liver disease and chronic alcohol use, or chronic hepatitis B or C may have a higher predisposition for DILI. This depends on the specific drug causing the injury; however, it often involves abnormal activation or inhibition of cytochrome p450 enzymes, increased inflammation, or increased production of a hepatotoxic metabolite [14, 15]. Though these are proposed mechanisms, there are no randomized controlled trials specifically comparing HDS use among patients with normal liver function and those with CLD to detail the difference in HDS metabolism between these populations.

Our study also showed that 3 respondents have admitted to taking GTE, a population size of 69,9998. Green tea is made from the unfermented leaves of Camellia sinensis, composed of several polyphenolic compounds (catechins), and can be concentrated into a GTE, which, in turn, is a common ingredient in many dietary supplements. Epigallocate-chin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE. GTE undergoes methylation in the liver, which has the potential to be disrupted in patients with CLD; however, the effect of this has not yet been fully studied. This may reflect concerns regarding a risk for hepatotoxicity with EGCG, especially where such risk may be unpredictable due to differences in EGCG's disposition in this patient population due to the underlying liver disease. Alteration in the expression of hepatobiliary transporter induced by liver disease may lead to difference in drug disposition. [15] Regardless, it is paramount that HCP encourage patients with CLD to disclose any use of HDS products and inform them of the potential for toxicity and, consequently, adverse clinical outcomes. Furthermore, it is imperative to investigate dietary supplements' pharmacokinetic testing in patients with a history of CLD.

It is important to note that many patients with CLD were taking non-hepatotoxic, over the counter HDS. Research is now being done on the benefits of HDS products for certain disease processes. Silymarin, a component of milk thistle seeds, has been related to decreased liver-related mortality in patients with cirrhosis due to its ability to act as a free radical scavenger [9].

Sho-saiko-to, a mixture of herbal supplements traditionally used in Asian countries, has been shown to decrease the rate of development of hepatocellular carcinoma (HCC) in patients with cirrhosis and increase survival of patients with HCC by inhibiting activation of stellate cells and preventing progression of fibrosis [10]. However, few products have been evaluated in well-designed, double-blind, controlled trials, so there is a lack of meaningful evidence to support their benefits, making it important for providers to fully explain the risks and benefits to patients with CLD.

Our study highlights the importance of obtaining a thorough history from patients with CLD. As most of these patients' report use of HDS, it is crucial for HCP to stay informed regarding side effects and provide proper counseling to their patients about safe use. Our study was limited by potential recall bias in the respondents, as they may not have remembered which supplements they were taking at the time or may have been unaware of some ingredients. It is also an older data set, with data from 2001-2011. As HDS use has continued to rise, our results could be different with a more recent set of data. The aim of this review was to highlight the gap in our knowledge on the consumption of hepatotoxic HDS in patients with CLD. As demonstrated above, there is a crucial need for more robust reporting processes of adverse hepatotoxic effects of HDS seen by practitioners, further studies regarding likelihood of hepatotoxicity of certain FDA approved HDS, and physician advocacy for increased scrutiny regarding ingredient and health benefit claims of HDS.

References

[1]. Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. Gastroenterology. 2015;148(3):517-32 e3.

[2]. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. Am J Epidemiol. 2004;160(4):339-49.

[3]. Mishra S, Stierman B, Gahche JJ, Potischman N. Dietary Supplement Use Among Adults: United States, 2017-2018. NCHS Data Brief. 2021(399):1-8.

[4]. Navarro VJ, Lucena MI. Hepatotoxicity induced by herbal and dietary supplements. Semin Liver Dis. 2014;34(2):172-93.

[5]. Ashar BH. The dietary supplement health and education act: time for a reassessment: comment on "acute selenium toxicity associated with a dietary supplement". Arch Intern Med. 2010;170(3):261-3.

[6]. "FDA and Clinical Drug Trials: A Short History," in A Quick Guide to Clinical Trials, Madhu Davies and Faiz Kerimani,: BioPlan Associates, Inc; October 2016.

[7]. Young AL, Bass IS. The Dietary Supplement Health and Education Act. Food Drug Law J. 1995;50(2):285-92.

[8]. 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(1):55-68.

[9]. CDC. National Health and Nutrition Examination Survey

[10]. Navarro VJ, Barnhart H, Bonkovsky HL, Davern T, Fontana RJ, Grant L, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014;60(4):1399-408.

[11]. Ghabril M, Ma J, Patidar KR, Nephew L, Desai AP, Orman ES, et al. Eight-Fold Increase in Dietary Supplement-Related Liver Failure Leading to Transplant Waitlisting Over the Last Quarter Century in the United States. Liver Transpl. 2022;28(2):169-79.

[12]. Kwon J, Kim S, Yoo H, Lee E. Nimesulide-induced hepatotoxicity: A systematic review and meta-analysis. PLoS One. 2019;14(1): e0209264.

[13]. Maddukuri VC, Bonkovsky HL. Herbal and dietary supplement hepatotoxicity. Clin Liver Dis (Hoboken). 2014;4(1):1-3.

[14]. David S, Hamilton JP. Drug-induced Liver Injury. US Gastroenterol Hepatol Rev. 2010; 6:73-80.

[15]. Halegoua-De Marzio D, Kraft WK, Daskalakis C, Ying X, Hawke RL, Navarro VJ. Limited sampling estimates of epigallocatechin gallate exposures in cirrhotic and noncirrhotic patients with hepatitis C after single oral doses of green tea extract. Clin Ther. 2012;34(12):2279-85 e1.