



Herbal and dietary supplements hepatotoxicity: Prevalence, Epidemiology and Key Issues

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Abstract

Herbal and dietary supplements (HDS) are widely utilized worldwide as supplementary and alternative medicine modalities that can cause hepatotoxicity. HDS consists of nutrients, minerals, or additional plant materials and substances derived from such plant life. They're being taken by oral route and intended to augment one's diet and improve one's health and properly-being. There's a bent for false reporting the amount of food they consume through patients and the significance of their utilization is under-recognized by physicians, although no single causality evaluation method is ideal for hepatotoxicity caused by HDS. The most extensively used method is the Roussel Uclaf Causality Assessment Method defining epidemiology, defining an acceptable nomenclature, and identifying culprit ingredients, predisposing host characteristics, and useful biomarkers are all things that need to be addressed for harm must all be priorities in the future. Herbal medicines have long been thought to be safe by people because they've been utilized for thousands of years in disease treatment despite potential toxicity, particularly "drug-induced liver injury" (DILI). Despite the risk of side effects, herbal medications have become increasingly popular around the world due to a lack of regulatory oversight.

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Introduction

Herbal medicine can be traced back to 2100 BC in ancient China and India (Schuppan *et al.*, 1999}. Herbal therapy is increasingly utilized in the treatment of many diseases, in the Eastern and Western worlds. The market for the natural dietary supplement (HDS) is accounting for \$180 billion in the United States, with an increasing percentage that reached 18.9%, people in the USA are using HDS despite their unproven therapeutic effectiveness by thorough and systematic testing (Navarro, 1999; Verma, Thuluvath, 2007).

According to the World Health Organization, traditional medicines account for over 40% of all healthcare services in India and Ancient China, whereas up to 80% of Africans still use traditional medicine to address their healthcare needs. Treatments like these are also available. They are fast gaining traction in more affluent countries, where they are referred to as complementary alternative medicine (CAM) (Aljofan, Alkhamaiseh , 2020). Garlic, Biloba, echinacea, ginseng, ginkgo saw palmetto, green tea, and grape seed extract were mostly used in herbal remedies. John's wort, bilberry, and aloe are used for the treatment of various diseases (Bent, Ko, 2020). For instance, as stated by 30–62 percent of patients who swallowed silymarin, the usage of HDS is widespread in people with chronic liver disease (milk thistle) (Verma, Thuluvath , 2007). This cohort is thought to be more vulnerable to hepatotoxicity and more prone to experience severe hepatic side effects.

The majority of HDS is given orally, where they are absorbed in the small intestine, enter the portal stream, and eventually metabolized in the hepatocytes of the liver through phase 1 metabolism (oxidation/hydroxylation process) catalyzed by cytochrome P450 enzymes, and to boost their water solubility, this phase I metabolites go through more metabolic phase 2 alterations. These Phase II metabolites are subsequently released from the hepatocytes to the bloodstream to be excreted in the urine, or to the bile through phase 3 metabolism to be

excreted in feces (Abdel-Qaderet *al.*, 2020). In addition, almost half of the respondents (50.6%) said they used herbs based on the advice of their families and friends. The media has a significant impact, as 30% of respondents said they followed media (conventional or social) advice on herbal supplement (HS) use. Only 8% of people are encouraged to utilize HS by their doctors. However, 86 % of herb users did not inform their dentists about their use of herbs HS use (Al-Zughaibi *et al.*, 2016).

This review article is concentrated on the potential hepatotoxicity of herbal and dietary supplements, prevalence, epidemiology and key issues.

HDS Hepatotoxicity

The demography of liver damage because of HDS is, unknown to a significant extent but is probably to be highly encouraged by sort of acceptability in terms of supplement, geography and culture. The real incidence and occurrence of hepatotoxicity because of HDS cannot be expected due to the denominator isn't available, the wide variety of humans in they are consumed by the population Estimates that are accurate totally on income are hindered using the numerous places in which you can attain HDS, consisting of health meals shops, Gyms, and the Internet. However, natural products induced hepatotoxicity could not be confirmed in a population-based potential 2-year cohort study in Iceland, where HDS accounted for sixteen percent of cases decided (Björnsson *et al.*, 2013).

Generally, 30–40% of patients revealed that they did not inform their doctors about their usage of HDS (3). HDS products are a term that is used for a variety of purposes, including weight loss, muscle building, immune support, and general well-being (Aljofan, Alkhamaiseh, 2020) (Figure 1).

Most of the respondents used herbs based on the advice of their families and friends, whereas media has a great impact, few people (8%) are encouraged to utilize HS by their doctors. On the other hand, 86 % of HDS users did not inform their doctors about their

use of herbs as shown in Figure 2 (Al-Zughaibi *et al.*, 2016).

HDS investigations showed that five to ten percent of patients suffered from drug-caused acute liver failure (ALF) (Reuben *et al.*, 2010; Russo *et al.*, 2004). Moreover, herbal merchandise is suspect a reason of hepatotoxic in 2–11 % of sufferers of Drug-induced liver injury (DILI) (Andrade *et al.*, 2005; Strader *et al.*, 2012; Woo *et al.*, 2021; Chalasani *et al.*, 2008; Ibanez *et al.*, 2021; Soares *et al.*, 2021) and even though an only center experience has suspected as HDS up to 70% of sufferers from ALF (Estes *et al.*, 2003). These numbers replicate the value of herbal hepatotoxic in medical exercise, and it must be

emphasized that the incidence of the disease is likely to be understated.

The spread of liver damage because of HDS is identical to DILI (drug-induced liver injury) It might range from a minor increase in liver function enzymes to abrupt liver failure. The bodybuilding industry is one of the HDS linked to hepatotoxicity.

The maximum common purpose of liver damage (Fig.2). Histologically because of HDS in maximum occurrences is a different type of medication and/or toxin-induced liver damage are indistinguishable. Medical-history-specific styles had been defined for a few HDS merchandise (Strader *et al.*, 2012).

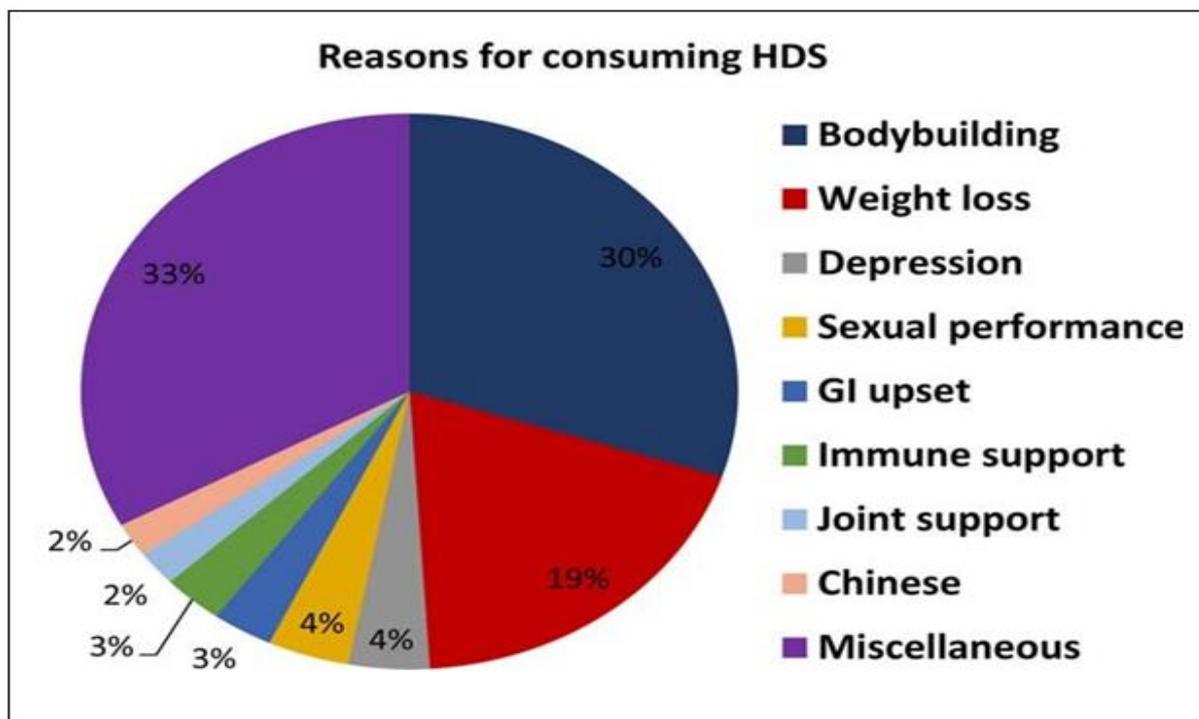


Fig. 1. Patients included in the US DILIN network had a variety of causes of taking herbal and dietary supplements (HDS) (based on data from Aljofan, Alkhamaiseh, 2020).

Extensive jaundice and intense itching are typical symptoms of those who get a liver injury as a result of bodybuilding HDS (Vinaya, *et al.*, 2014). In addition, "other or non-bodybuilding" HDS products were found to induce more hepatocellular-type liver damage. Eighteen patients who have had liver damage as a result of body-building HDS have a better outcome than those who have had a liver injury as a result of various HDS. These patients can be

treated with the usual methods (Vinaya *et al.*, 2014). According to the findings, mortality was occurred in 4%, whereas in 13% liver transplantation was occurred in patients with liver damage caused by non-body-building HDS merchandise. Nine Compared to DILI caused by regular tablets, the necessity for liver transplantation has increased in individuals with liver damage caused by non-bodybuilding HDS products. The fact that herbal supplements sometimes include

many substances and are frequently used concurrently makes determining a real incidence of HILI problematic. As a result, determining specific HDS contents are responsible for hepatotoxicity is difficult, if not impossible. Supplement mislabeling and patient non-disclosure and medical ignorance all add to the difficulty of diagnosing HILI. HILI, on the other hand, must be kept in mind by doctors because it has a higher risk of acute liver failure than DILI (Woo *et al.*, 2021).

Socio-demographic characteristics influencing the herbal medicine practices

In one of the Studies, in Makkah, HS is being used by adult dental patients. Among those that responded, 79 percent said they use HS. This is higher than what earlier research on the use of HS by dental patients has reported (ranges between 12.6 to 54 %). The disparity in reported HS consumption rates could be explained by the variation in the population investigated, as well as the effect of culture and ethnic background (Al-Zughaibi *et al.*, 2016). In addition, it was HS use is more widespread in middle age, among women, among individuals with a high school degree or more, and among those who are currently using over-the-counter (OCT) or prescription medication, according to the study. And friends and family were the main sources of advice regarding HS use. Mint was the most often utilized herbal supplement, followed by ginger, green tea, and garlic in that order. Other herbs have also been recorded to be regularly used in the literature. Echinacea, Ginkgo biloba, and Ginseng are some of the herbs used by dental patients (Al-Zughaibi *et al.*, 2016). The majority of participants believed HS were safe and had no negative effects, which is consistent with earlier data, and 86% did not tell their dentist about their usage of HS. Furthermore, 96 percent of herbal users lacked written documentation about their use of HS.

Diagnosis and causation evaluation

It became necessary to have strong indications of suspected hepatotoxicity resulting from the use of herbs, which led to DILI. Patient history should include the use of herbal products, especially for

patients with any type of acute or chronic liver disease. Additional information on natural processing taken, amount and time, and also the identical drugs.

In some cases, studying the label of herbal goods and substances included. It's possible that some of the ingredients were combined in the preparation beneficial. A listing of vital diagnostic factors it has been suggested that the DILI analysis be used to rule out alternative factors of hepatic impairment and to improve the viability of the DILI analysis, which will improve the nice and scientific use of drug toxicity reports. (Agarwal *et al.*, 2010) Acute hepatitis E has been linked to a few cases of DILI, (as much as 13% in developed international locations, and all likelihood a good deal higher in growing international locations) and consequently test for hepatitis E antibody finished if clinical capabilities similar to acute viral hepatitis (Dalton *et al.*, 2007; Davern *et al.*, 2011). The opportunity of natural hepatotoxic superimposed on pre-existing liver ailment need to additionally be considered, in particular these treatments used by patients suffering from chronic liver disease, and in this case, it's miles extra difficult to make a simple analysis. Although liver histology is frequently non-unique, it can be informative in a few circumstances. Uncommon necrotic lesions with steatosis, histological zonal necrosis, and bile duct injury are examples of liver injury patterns. Vascular damage must raise suspicion of spontaneous hepatotoxicity, especially veno-occlusive disease (VOD) (Schiano, 2003).

The most common clinical manifestation was jaundice, which was in 437 (46.3 %) of the cases studied also abdominal pain and nausea were present (22.4 % and 17.2 %, respectively). 131 (13.8 percent) of the patients had hepatomegaly and tiredness, while 120 (12.7%) had acholuria. In most cases, liver function and damage tests revealed significant changes in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were high 22 and 28 times their respective upper limit of normal (ULNs), respectively, and alkaline phosphatase (ALP) was double to its normal range (Ballotin *et al.*, 2021).

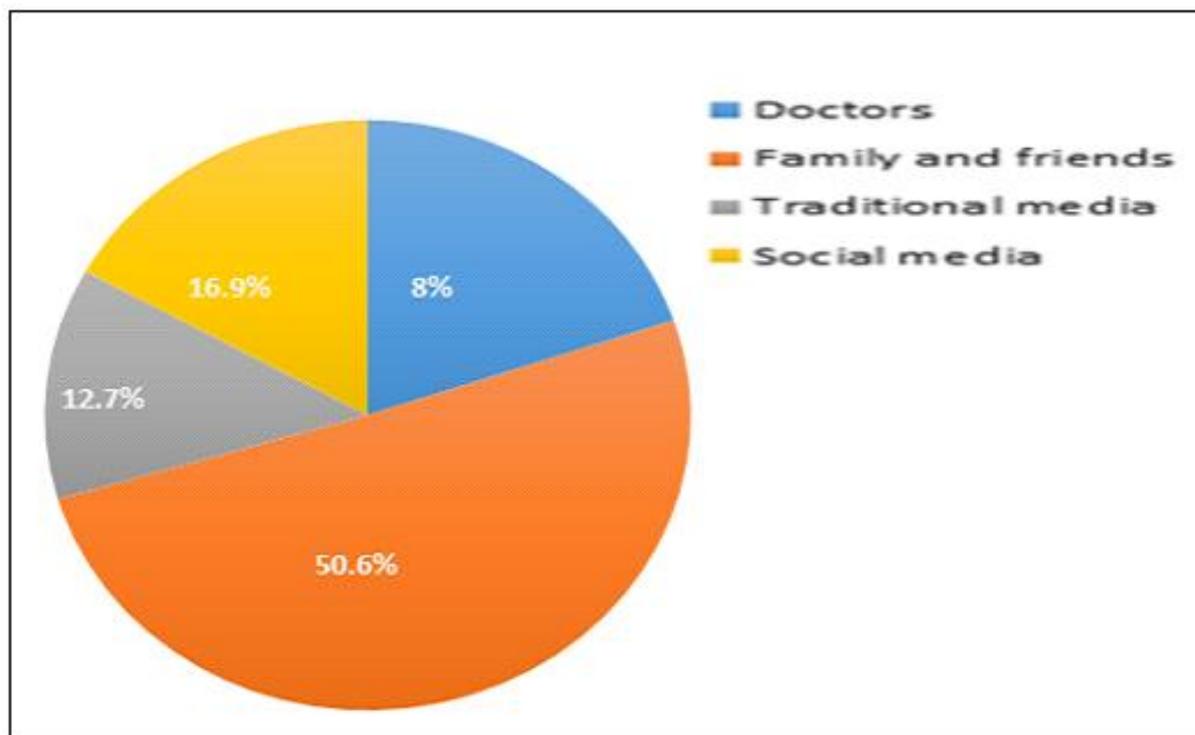


Fig. 2. Source of advice on HS use (from Al-Zughaibi *et al.*, 2016).

The Roussel Uclaf Causality Assessment Method (RUCAM) of the Council for the International Organization of Medical Sciences (CIOMS) (Benichou, 1990) and Maria and Victorino's clinical scale are the most common scoring systems in assessing the causality assessment of DILI (Maria, Victorino, 1997). RUCAM, on the other hand, is a flawed instrument, and some writers think that it should be improved because several of its criteria are not supported by evidence (Woo *et al.*, 2021).

Regarding the grade found after using RUCAM in the studies, the majority of the instances were categorized as possible or probable. Due to low or negative scores, RUCAM's retrospective case review results in low scores and lower causality classifications, indicating insufficient robustness (Soares *et al.*, 2021).

The CIOMS scale is probably the most popular of these rating systems and is used within the literature (Chalasan *et al.*, 2008; Benichou, 1990). It applies to interest in key capabilities in 7 exclusive domains namely: chronology (de-challenge and latency), danger causes, concomitant drug use, exclusion of different reasons, preceding records on drug's

hepatotoxicity capacity, and reaction to rechallenge. Every score given to each area is added together to produce a total score that measures the causation possibility of DILI; specific, very probable, probably, viable, not going, or excluded (Benichou, 1990).

The CIOMS scale, whilst to begin with confirmed, tested perfect reproducibility and overall performance, with 93% high-quality predictive price and 93% terrible predictive fee (Benichou *et al.*, 1990). However, further validations have cast doubt on the approach's reliability, and there have been several difficulties in using the rating in medical practice (Rochon *et al.*, 2008; Shapiro, Lewis, 2007).

Herbal products, unlike conventional treatments, usually contain several components. As a result, their pharmacological properties and safety are unknown. The majority of patients use them to improve their overall health, maintain their health, and lose weight. HILI symptoms can range from no symptom's instances related to elevated transaminases to liver failure patients requiring liver transplantation or death, depending on the causative product (Ballotin *et al.*, 2021).

Despite the ancient usage of traditional medicines by various populations, it was only later that a legal process began to provide their legitimacy within a legal framework. Regulative precedent, on the other hand, is difficult to establish. In 1974, the World Health Organization (WHO) recommended underdeveloped countries to use herbal medicine to "meet the demands that had not been met by contemporary medicines." The Diet Supplementary Health and Education Act (DSHEA) was formed in 1993 after the Food and Drug Administration (FDA) evaluated herbal supplements and products. It issued the "last Rule: Dietary Supplement Manufacturing: Current Good Manufacturing Practices, Packing, Labeling, or Holding Operations" in 2007, issued the "last Rule: Current Good Manufacturing Practice in Dietary Supplement Manufacturing, Packing, Labeling, or Holding Operations" (Valdivia-Correa *et al.*, 2018).

The main issue that regulators are dealing with is that the precautions for using herbal medications can be misleading for some people because these items are classified as "naturally occurring" rather than "man-made" substances. Furthermore, they are available without a doctor's prescription in a variety of forms, including teas, capsules, and tablets. Misidentification of plants, as well as the inclusion of pollutants, impurities, and adulterants in herbal products, are still major issues. (Valdivia-Correa *et al.*, 2018).

Regardless of stringent law, Damage from HDS will occur with rigorous adherence and attentive observation, just as it does with standard drugs. As a result, biomarker discovery to predict or anticipate liver damage at an early stage should be pursued. Alkaloids and germander were used to find biomarkers for liver injury caused by HDS, (De Berardinis *et al.*, 2000; Gynura *et al.*, 2011) presenting cause for extra studies in this area.

Conclusion

In conclusion, the idea that HDS are harmless can be questioned, as there's adequate proof to the opposite.

Associating damage phenotypes with product kinds becomes easier because of a new machine for categorizing HDS. Herbal remedies are widely utilized in underdeveloped nations, and scientific evaluation of all specimens will be impossible shortly. Although some herbal treatments are thought to be harmless, several of them can cause serious liver damage. It's impossible to know how common HILI is, and it's likely underreported. Therefore, to decide the maximum relevant taxa and their harmful effects from a pharmacological standpoint, ethno pharmacological and toxicological research, as well as rigorous Separation of merchandise into their numerous components, is required. From a clinical standpoint, we must advance in our recognition of signs and symptoms that indicate a problem with liver function because the prognosis for acute liver failure can be improved with a differential diagnosis. Patients and doctors must be educated, especially when it comes to clarifying and emphasizing that "now not all-natural merchandise are secure." These factors have the potential to regulate the hassle's attitude. Awareness and need assessment have to be understood locally about cultural, traditional, and geographical distribution and availability and accessibility and cost-effectiveness of herbal products. Most of the general population are using herbal supplements during Pregnancy as the safe alternative, chronic allergic disorders, metabolic disorders like diabetes, sexual disorders, and kidney impairment. Reasons for usage of HS are easy and over-the-counter availability cost-effective and prejudiced about its safety and free of side effects. So, community need-based interventional programs to be implemented to create awareness and analyze the hidden epidemic and exact prevalence and positive and negative graded potential of dosage of herbal supplement to understand its limitations.

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