Herbal and Dietary Supplement Hepatotoxicity

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Overview

Herbal and dietary supplements (HDS) are the most common form of complementary and alternative medicine used in the United States.[1] American consumers spend about $6 billion on HDS yearly.[2] HDS include vitamins, minerals, herbs or other plant materials, and materials extracted from such plants. They are taken by mouth and are intended to supplement the diet and enhance health and well-being. HDS are consumed by about one-half of the US population, and their use has been on the rise over the past several years.[3] HDS can cause hepatotoxicity. The estimated incidence of HDS hepatotoxicity has risen almost threefold over the past decade (Fig. 1).

Drug and HDS Metabolism

The human liver and kidneys metabolize and excrete a wide array of drugs and chemicals, which are either introduced from outside (xenobiotics) or generated endogenously (hormones, chemokines, cytokines). The metabolism of xenobiotics or endogenously produced compounds by the liver is a complex, multistep process. Most drugs or HDS are taken orally, absorbed primarily in the proximal small bowel, enter the portal circulation, and reach the liver where they undergo "first-pass metabolism." Most drugs or components of HDS undergo an initial hydroxylation/oxidation reaction (phase 1 metabolism) after entering the hepatocytes, which is catalyzed by cytochrome P450 enzymes. They subsequently undergo additional changes (phase 2 metabolism) to increase their water solubility. The metabolites are eventually transported out of the hepatocytes (phase 3 metabolism) and into the bloodstream (to be excreted in urine) or into the bile (to be excreted in feces).

In addition to their potential therapeutic benefit, drugs and HDS can result in several side effects or adverse reactions (ARs) involving one or more organ systems. Drug- or HDS-induced liver injury is one of the major ARs caused by such chemicals. The pathogenesis of liver injury due to most drugs or HDS [DILI] is not completely understood. A complex and variable interplay of features related to the drug or chemical, host, and environmental factors likely occurs in most instances (Fig. 2). Some drugs and chemicals are known, dose-dependent hepatotoxins. The best known and most important of these is acetaminophen (aka paracetamol). It will cause liver injury in any animal or human who takes a sufficient dose, and its metabolic activation to a highly reactive, potentially toxic quinoneimine (NAPQI) intermediate has been widely studied.[6] It is a prototypical "intrinsic" hepatotoxin. However, many more drugs only rarely cause DILI (1/1000 to 1/1,000,000) and without clear dependence on dose or duration of drug use. For many drugs, reactive metabolites are probably involved, but the pathogenesis appears to involve idiosyncratic host immune responses to metabolic particularities. Such drugs are said to cause "idiosyncratic" DILI. Clinicopathologically, DILI can present as hepatocellular, cholestatic or mixed patterns—or as hepatic steatosis. The spectrum of hepatic injury can vary from mild, asymptomatic, liver test elevation to acute liver failure causing death or requiring liver transplantation.

HDS Use and Surveillance Systems.

The US Food and Drug Administration (FDA) collects and maintains a large database of ARs voluntarily reported by practitioners and those in pharmaceutical industry (eg, Medwatch). Unfortunately, such mechanisms do not exist for HDS. Patients tend

Abbreviations: ARs, adverse reactions; DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; FDA, US Food and Drug Administration; HDS, herbal and dietary supplements; NAPQI, N-acetyl-p-benzoquinoneimine.

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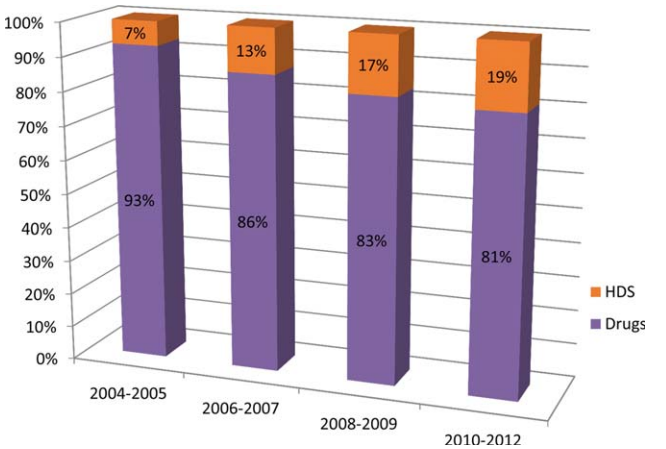

Figure 1 Rising incidence of liver injury due to herbal and dietary supplements (HDS) over the past decade. Data are from the US Drug-Induced Liver Injury Network database, as reported at the Annual Meeting of AASLD, November 1-5, 2013, Washington, DC.[4]

to underreport their HDS use to their physicians. According to Verma et al, about 31% to 40% of patients do not disclose HDS use.[2] HDS products are consumed for multiple purposes such as weight loss, bodybuilding, immune support, general well-being, etc (Fig. 3). Previous studies have indicated that the prevalence of HDS use, even among individuals with chronic liver disease, is about 40%.[7] These individuals may be at a higher risk for developing HDS liver toxicity compared to the general population. Certainly, if they do develop toxicity, they are at increased risk of having adverse outcomes.

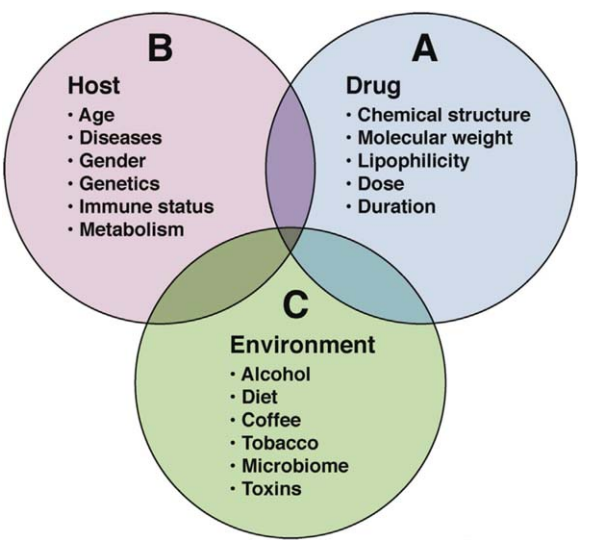

Figure 2 Pathogenesis of idiosyncratic DILI. Diagram representing complex interplay among host, drug, and environmental factors.From Fontana[5] with permission of the author and publisher.

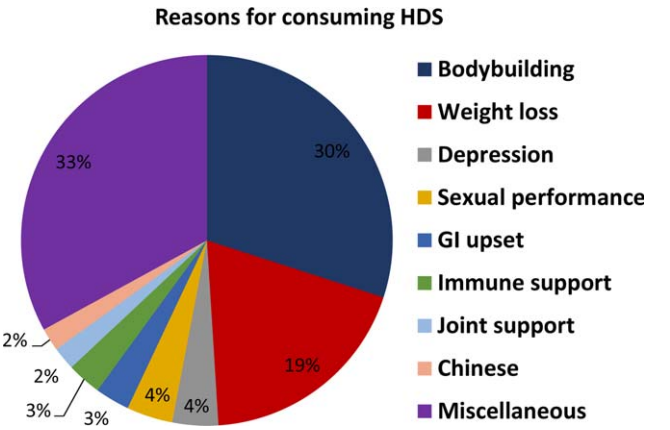

Figure 3 Reasons for consuming herbal and dietary supplements (HDS) in patients enrolled into the US DILIN network.[4]

HDS products are often marketed as complex mixtures containing several ingredients. The exact biologic role of each individual component in a mixture is difficult to ascertain. The concentrations and biologic activity of the ingredients can also vary from batch to batch within the same product by the same manufacturer. In addition, HDS products are sometimes adulterated with prescription drugs such as steroids, thyroid hormones, phosphodiesterase inhibitors, phentermine, etc.[9] In addition, because they are heavily promoted as being "natural," they are perceived to be "safe" by consumers. Unlike prescription drugs, HDS are not stringently regulated by the FDA. Indeed, under current statutes, the FDA may not take action to limit distribution of HDS until after they have been found to cause ARs.

TABLE 1 Herbs and Associated Liver Injury

HDS	*Nature of Liver Injury*
Atractylis gummifera	Diffuse hepatic necrosis
Black cohosh	Elevated liver tests, liver failure
Camphor	Elevated liver tests, Reye syndrome
Cascara	Bridging fibrosis, bile duct proliferation
Chaparral	Cholestasis, zone 3 necrosis
Chaso (and onshido)	Elevated liver tests, liver failure
Greater celandine	Cholestasis
Germander	Zone 3 necrosis, cirrhosis
Green tea extracts	Acute hepatitis, hepatocellular injury
Impila	Hepatic necrosis
Ju bu huan	periportal fibrosis, steatosis
Kava	Elevated liver tests, liver failure
Ma huang	Elevated liver tests, liver necrosis
Mistletoe (skullcap, valerian)	Elevated liver tests, acute hepatitis
OxyElite Pro (aegeline)	Acute hepatitis, liver failure
Noni juice	Acute hepatitis, liver failure
Pennyroyal	Acute hepatitis, liver failure
Pyrrolizidine (comfrey, mate, bush tea)	Veno-occlusive disease
Sho-saiko-to (dai-saiko-to, TJ-9)	Bridging fibrosis, steatosis

This table has been adapted and modified from Zakim and Boyer.[1]

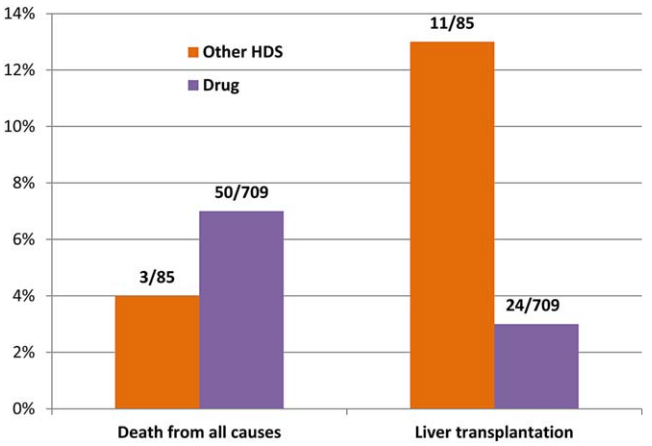

Figure 4 Difference in all-cause mortality and liver transplantation in liver injury due to "other" HDS and conventional drugs.[4]

HDS Hepatotoxicity. The incidence of liver injury due to HDS appears to have risen about threefold in the US during the past decade (Fig. 1). This is probably due in part to the growing consumption of HDS products. Among the patients enrolled into the prospective Drug-Induced Liver Injury Network (DILIN), HDS as a group are the second most common cause of drug-induced liver injury.[10] Among HDS implicated in hepatotoxicity, the bodybuilding products are the single most common cause of liver injury (Fig. 3).

The spectrum of liver injury due to HDS is similar to DILI and varies from mild elevation in liver tests to acute liver failure. Histologically, liver injury due to HDS in most instances is not distinguishable from other forms of drug and/or toxin-induced liver damage. Specific clinical-histologic patterns have been described for some HDS products (Table 1). Patients who develop liver injury due to bodybuilding HDS typically have prolonged jaundice and severe itching.[4] In contrast, "other or nonbodybuilding" HDS products typically cause a more hepatocellular-type of liver injury.[4] Patients with liver injury due to bodybuilding HDS have a better prognosis compared to those with liver injury due to other HDS, and they generally improve without the need for liver transplantation.[4] In contrast, the all-cause mortality was 4%, and liver transplantation was required in 13% of patients with liver injury due to non-bodybuilding HDS products.[9] The need for liver transplantation was higher in patients with liver injury due to non-bodybuilding HDS products compared to DILI due to conventional drugs (13% vs 3%) (Fig. 4).

In summary, HDS are widely used and their use is on the rise. They are perceived to be safe, but they can cause severe liver injury. The exact incidence of HDS-induced liver injury is difficult to ascertain, but it is probably underreported. Liver injury is generally hepatocellular, but bodybuilding HDS may also cause a cholestatic pattern of injury. Attribution of liver injury as being due to HDS (or to drugs) is a diagnosis of exclusion. Causality is difficult to establish because of the complex nature of the marketed HDS products. Improved regulatory mechanisms are required to oversee all aspects of the HDS industry in order to better protect the consumers and prevent HDS-induced adverse events. ■

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