

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Supplements and Hepatotoxicity



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G&H Why are supplements a concern among people who treat liver conditions?

KRR Whether they are healthy or ill, many people take a variety of complementary and alternative medications, including herbal and dietary supplements. Such supplements are available for a wide array of conditions, and many people report that their health improves after taking supplements. However, while there may be potential benefits to herbal and dietary supplements, there may also be toxicity issues, including liver toxicity.

G&H What are the specific types of liver toxicity that have been observed?

KRR Herbal and dietary supplements are associated with a wide range of hepatic issues. Patients can develop jaundice, cholestasis, or liver failure. Some people experience mild hepatitis, while others may need a liver transplant, although rarely.

G&H How common are these side effects?

KRR The exact incidence is not known, mainly because herbal and dietary supplements are not regulated in the same way as medications. Most of the data on supplement-induced hepatotoxicity come from case reports, case series, retrospective reports, and the US Drug-Induced Liver Injury (DILI) Network. However, some reports exclude herbal supplements when tallying the causes of these side effects.

That being said, the available data indicate a hepatotoxicity incidence rate of approximately 2% to 11% among patients with DILI and 5% to 10% in patients with drug-induced acute liver failure. In a single-center study, Estes and colleagues found that 10 of the 20 patients referred for liver transplantation due to fulminant hepatic failure were actively using supplements or herbs that were previously associated with hepatotoxicity. Of these 10 patients, 7 appeared to have no other underlying cause for hepatic failure. It should be noted, however, that the number of deaths among the supplement users and nonsupplement users undergoing transplantation for liver failure was the same.

G&H What supplements are associated with hepatotoxicity?

KRR Bodybuilding reagents and weight-loss supplements are the most common causes of supplement-induced hepatotoxicity.

Two recent cases of severe hepatotoxicity were associated with Herbalife products contaminated with *Bacillus subtilis*, and Hydroxycut has been connected to cases of hepatocellular and cholestatic liver injury, as well as acute liver failure requiring liver transplantation. Hydroxycut products were recalled by the manufacturer in 2009 after receiving a warning from the US Food and Drug Administration (FDA) but have since been reformulated and released.

Green tea is a common ingredient in weight-loss supplements. In a 2009 review, Mazzanti and colleagues found an association between green tea and liver damage.

The liver injury pattern was hepatocellular in nature in most of the cases, but some patients also experienced cholestasis or a combination of hepatic issues. However, it is important to note that other studies have shown that green tea plays a role in cancer prevention, hepatoprotection, and overall health.

G&H Is it difficult to diagnose supplement-induced liver injury?

KRR Yes, it can be quite difficult to diagnose supplement-induced liver injury. Herbal preparations are not comprised of merely 1 compound or a single agent. They are made up of a mixture of ingredients, and there can be contamination in the background by unidentifiable agents. It can also be quite challenging to determine which of the multitude of ingredients is actually causing the toxicity.

In addition, there is not currently a causality tool set up to diagnose herbal hepatotoxicity, although there is a causality process for DILI in general, in which the various known causes for hepatitis or jaundice can be eliminated. The Council for International Organizations of Medical Sciences' (CIOMS) Roussel Uclaf Causality Assessment Method is a commonly used system for determining the causality probability of DILI. Seven weighted categories, such as risk factors and elimination of other factors causing liver injury and of concomitant potentially hepatotoxic medication use, are used in this system. However, no score is assigned for products that have not been previously identified as hepatotoxic, and because herbal supplements are not regulated to the same degree as other pharmaceutical agents, the propensity for each active ingredient to trigger liver problems is often not known for a given product. All of these issues render the CIOMS scale less useful than it could be.

A group of researchers from the US DILI Network has proposed a new assessment tool for evaluating herbal and dietary supplements, but further investigation is needed.

Clinicians should always ask patients about any supplements or herbal products being taken. The recorded information should include the exact preparation, dosage, and duration of use, along with other medications being taken at the same time. Because supplements can interfere with a variety of drugs and can cause various interactions, the clinician may want to review the label on the supplement bottle in order to identify any potentially concerning ingredients.

G&H Is there a connection between Ayurvedic products and hepatotoxicity?

KRR Ayurveda is an ancient practice that originated in India. It uses a variety of approaches; not only supplements, but also herbs, metals, and minerals may be used.

Heavy metal poisoning has been a concern with Ayurvedic products. A 2005 study found detectable levels of lead, mercury, or arsenic in 20% to 22% of Ayurvedic medications purchased online. However, hepatotoxicity from Ayurvedic medicine is not often noted in the literature. One case study reported severe hepatitis in a woman who treated her vitiligo with Ayurvedic herbal products for 9 months. A European randomized controlled trial of the Ayurvedic herbal combination known as Liv.52 showed a potential risk for liver-related mortality, although the enrolled patients had alcohol-related cirrhosis.

G&H Has hepatotoxicity been linked to Chinese herbal medicines?

KRR Jin Bu Huan (*Lycopodium serratum*), an herb taken for its sedative and analgesic effects, has been associated with liver injury—specifically, acute hepatitis. One case study reported chronic hepatitis linked to this herb.

Ma huang (*Ephedra sinica*) has demonstrated a risk of severe hepatitis and acute liver failure. This herb, used for nasal decongestion, bronchodilation, and weight loss, is an ingredient in other weight-loss products that have been associated with hepatotoxicity.

Other herbs used in Chinese medicine that have raised concern about liver issues include Dai-saiko-to, geniposide, and Shou Wu Pian.

G&H What other plants commonly found in supplements have been linked to hepatotoxicity?

KRR Thistle (*Atractylis gummifera*) has been used for its antipyretic, antiemetic, abortifacient, and diuretic properties. However, there have been numerous reports of liver injury associated with this plant, particularly in children. Side effects can manifest within hours of consuming this supplement and may include vomiting, abdominal pain, diarrhea, and eventually acute liver failure.

Chaparral (creosote bush or greasewood) has been used in patients with pain, bronchitis, and cancer, among other conditions. The supposed mechanism of action of this plant is thought to be linked to antimicrobial and antioxidant activities. The active ingredient, nordihydroguaiaretic acid, inhibits lipoxygenase and cyclooxygenase pathways. Side effects associated with chaparral include jaundice with an increase in alanine aminotransferase levels. According to a study by Sheikh and colleagues, among 13 patients with chaparral-induced hepatotoxicity, 2 required liver transplantation and 4 developed cirrhosis.

Greater celandine (*Chelidonium majus*) is another concerning plant with regard to hepatotoxicity. This plant contains many alkaloids and has been used in patients with biliary disorders and irritable bowel syndrome. There

have been numerous reports of liver injury in patients taking this plant. In a case series of 10 female patients, 5 experienced cholestasis (but not liver failure), and all had moderate increases in alanine aminotransferase levels. Oral greater celandine was banned in Germany and other European countries after reports of 40 incidents of hepatic injury triggered by the plant. In Australia, health authorities recommend that products with this plant carry a warning label and that people taking such products do so under the supervision of a medical professional.

G&H What challenges exist to the ongoing efforts to increase regulation of supplements?

KRR The greatest hurdle to increasing the monitoring of supplements is the fact that this is a large and extremely profitable industry. However, there are ongoing efforts to improve monitoring, both among academic researchers and among manufacturers. More information online would be useful for people who are considering using these supplements.

Education is also needed to increase the awareness of potential hepatotoxicity and to try to convince the FDA to

be vigilant about reported cases. The FDA has taken certain items off the market, but they often return under a different name, so it can be challenging to eliminate all of them.

Dr Reddy has no relevant conflicts of interest to disclose.

Suggested Reading

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