

Herbal medicine-related hepatotoxicity

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Abstract

Herbal medicine products represent a common therapeutic approach in the East and are gaining increasing popularity in Western countries. They are unjustifiably considered to be side-effect free; on the contrary, severe toxicity, including catastrophic hepatic injury has been reported in association with their use. Vigilance is

required from both physicians and the general public. Physicians should always suspect herbal medicines when evaluating a patient with unexplained liver injury. Regulation standards for herbal products need to be reconsidered, so that the efficacy and safety of these products have been clearly demonstrated before they enter the markets.

Key words: Herbal medicines; Liver transplantation; Cholestasis

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Core tip: Herbal medicine products represent a common therapeutic approach in the East and are gaining increasing popularity in Western countries. They are unjustifiably considered to be side-effect free; on the contrary, severe toxicity, including catastrophic hepatic injury has been reported in association with their use. Vigilance is required from both physicians and the general public. Physicians should always suspect herbal medicines when evaluating a patient with unexplained liver injury. Regulation standards for herbal products need to be reconsidered, so that the efficacy and safety of these products have been clearly demonstrated before they enter the markets.

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TEXT

The use of herbal products as medications has its origin thousands of years ago and has been documented in historical evidence from many ancient civilisations. In recent years, there has been a significant increase in the use of herbal medicines and herbal dietary supplements

in Western societies, mainly for body building, weight loss and maintenance of “good health”. This increased use is supported by a general belief among lay people, that since these products are natural, they are also harmless; this belief is, however, frequently inaccurate and mistaken. Indeed, herbal products have been reported to cause severe side effects. Among these, liver injury, occasionally severe enough to necessitate transplantation or lead to death, has been frequently described.

Herbal medicines represent a lucrative business in both Europe and United States. In 2003, more than \$5 billion has been spent on over the counter herbal products in Europe^[1]. A survey including 6 countries (United Kingdom, Spain, Germany, Italy, Romania, Finland) revealed that 18.8% of 2359 consumers had used plant food supplements at least once^[2]. In the United States, 100 million Americans spend \$28 billion each year in supplements^[3]. Data from National Health and nutrition examination survey reveals that 52% of the general population had consumed supplements between 1990-2000^[4]. This tendency towards constant increase in the use of herbal medicines has several explanations. Many people believe that conventional drugs cause severe side effects and are reluctant to use them. On the other hand, many believe that herbal medicines have been used for centuries, are effective, harmless and represent a more “natural” or “physiological” means of managing or preventing diseases. Moreover, marketing regulations for herbal medicine are considerably less strict than for conventional drugs and no safety or efficacy trials are required before these products are being marketed. This leads to an abundance of easily accessible herbal medicine products that are sold over the counter or *via* the internet. Herbal products in the United States are regulated by the dietary supplement health and education act (DSHEA), introduced in 1994^[5]. According to DSHEA, a dietary supplement is a product taken by mouth that contains an ingredient (vitamin, mineral, herb or other botanicals, aminoacid or substances such as enzymes, organ tissues, glandulars and metabolites), intended to supplement the diet^[6]. Manufacturers of herbal medicines are not required to get Food and Drug Administration (FDA) approval before selling a new product and they are responsible for non-misleading labelling, reporting any side effect and ensuring that their product has not been contaminated or adulterated^[3,5]. In European Union, for herbal medical products to be allowed entering markets, they need to have been used medicinally for at least 30 years in general and for at least 15 years in Europe and to have sufficient data that they are not harmful and that their pharmacologic effects are plausible^[1].

Herbal medicines are divided into 3 categories. First, there are plant-derived crude products, such as leaves, roots and flowers. Importantly, the exact ingredients and their concentrations in these products are unknown and are subject to harvest conditions, weather, altitude of growth and contamination with pesticides and heavy

metals. The second category comprises of botanicals, which have been the cornerstone of pharmaceutical industry growth. Famous paradigms include poppies-derived opioids, china bark from which quinine is extracted and mandrake, the source of atropine^[7]. The third category includes all commercially available products marketed under trade names and represents the majority of herbal medicines used in Western societies. Current lenient regulation standards often result in poor quality products; contamination with bacteria or heavy metals such as arsenic has been documented^[8,9]. In one case, a weight loss-inducing nutritional supplement contaminated with *Bacillus subtilis* caused severe hepatotoxicity in 2 patients^[9]. Mislabelling is another issue of concern; concentrations of constituents are often inaccurate and may vary from batch to batch. Adulteration with other substances such as steroids, benzodiazepines, sildenafil and others that do not appear on the ingredients list has also been reported^[10], and contributes to the emergence of side effects.

Herbal medicine-related hepatotoxicity represents the second most common cause of drug-induced liver injury (DILI) in Western countries. In a prospective study from Iceland that included 96 individuals diagnosed with DILI between 2010 and 2011, 16% of cases were attributable to dietary supplements^[11]. In the United States, the drug induced liver injury network, which studies liver toxicity related to the use of conventional medications or herbal supplements, constitutes the largest database of herbal medicines-related hepatotoxicity. Between 2004 and 2013, among 839 patients who had suffered DILI, herbal dietary supplement was identified as the culprit in 130 cases (15.5%)^[12,13]. Interestingly, the proportion of DILI caused by herbal medicines increased from 7% to 20% during this time period, reflecting the increasing popularity of these products. Supplements used for body building were the most commonly implicated (45 of 130 cases), followed by weight loss-inducing products. Chinese herbs and supplements for depression, gastrointestinal symptoms, sexual performance enhancement and joint problems were less commonly implicated in DILI. In another recent retrospective cohort study using data from a Northern California health care system between 2004 and 2014, 18.8% of cases of acute liver failure were caused by over-the-counter herbal supplements^[14]. In Europe, an earlier study performed between 1994 and 2004 in Spain reported that 9% of 461 cases of DILI were caused by medicinal herbs^[15]. Interestingly, herbal products also represent the most common cause of DILI in the East, reflecting their widespread use worldwide. In a prospective Korean nationwide study on DILI, “herbal medications”, “herbal preparations”, “medicinal herbs or plants”, “health foods or dietary supplements” and “folk remedies” were the causative agents of 232 of 371 reported cases of DILI (62.5%)^[16].

There are 3 patterns of drug (and herbal dietary supplement)-induced liver injury: hepatocellular, cholestatic, and mixed. The R-value is a helpful index for

distinguishing the type of liver injury at presentation. R-value is defined as patient's serum alanine aminotransferase (ALT)/upper limit of normal of ALT divided by patient's serum alkaline phosphatase (ALP)/upper limit of normal of ALP^[17]. When R is ≥ 5 , injury is classified as hepatocellular, when R is < 2 as cholestatic, and when R is 2-5 as mixed. With the exception of herbal supplements used for body building, which cause a cholestatic pattern of liver injury, most of the herbal products typically induce hepatocellular damage^[12,17].

A large number of herbal medicines have the potential to cause liver injury. Body building products typically cause cholestatic hepatic injury and affected patients are usually young males. Performance enhancing agents are the most commonly implicated agents in the drug induced liver injury network study. Such supplements typically contain steroids, whose hepatotoxicity potential has been well established^[13,18]. Greater celandine (*chelidonium majus*), used for the management of dyspeptic symptoms, and cascara sagrada, a herbal laxative containing anthracene glycoside, are 2 other herbal medicines that have been associated with cholestasis^[19,20]. The rising prevalence of obesity in Western societies has led to a flourishing market of weight loss-inducing herbal medicines, which are frequently implicated in cases of hepatotoxicity. Hydroxycut, a multi-ingredient product, marketed as a stimulator of basic metabolism and a lipolytic agent, was eventually recalled from the market by the manufacturer in 2009. Severe hepatocellular injury, leading to liver transplantation and even death, has been associated with this product^[21]. OxyELITE Pro has been shown to cause severe or even fatal hepatitis at the recommended dosage, leading the FDA to ban its sales in 2013^[22]. Herbalife products, used for a variety of purposes, including weight loss and general well being, have also been linked to severe cases of liver injury^[23]. Germander also appears to induce weight loss but also contains diterpenoids that cause hepatocyte apoptosis^[24]. Green tea is extracted from *Camellia sinensis* leaves and is commonly present in weight loss supplements. Although the consumption of average amounts of green tea appears to be safe, excessive doses found in dietary supplements have been associated with hepatocellular injury, induced by catechins^[25,26]. Extract from comfrey tea (*symphytum*), used to make tea, induces venoocclusive disease, since it contains pyrrolizidine alkaloids^[27]. Kava, extracted from *piper methysticum* and used for anxiety symptoms and sleep disorders, is particularly popular in the Pacific Ocean islands and has been incriminated in many cases of hepatotoxicity, leading to a ban of kava-containing products import in Europe and United States^[28]. Finally, black cohosh (*cimicifuga racemosa*), used for menopause symptoms and dysmenorrhea, and glucosamine-containing supplements, popular products marketed for joint pain relief, have also been associated with severe hepatotoxicity^[29-31].

Establishing a causal relationship between the use

of herbal medicines and liver injury is challenging. Even when highly suspected, direct correlation between a single causative agent and hepatotoxicity can be extremely difficult to prove. The variable composition of herbal products (according to weather and harvest conditions), the plethora of (often unlabeled) ingredients and contamination or adulteration may impede diagnostic approach and establishment of causality. Clinical suspicion that a herbal medication may have caused hepatotoxicity is fundamental for diagnosis. Patients tend to underreport consumption of herbal dietary supplements^[32], therefore physicians should persistently assess this possibility during history taking. Initiation of the suspected product prior to the manifestation of liver injury is also a major key point for establishing causality. Other non-pharmacological causes of liver injury must also be excluded. These include viral hepatitis (by hepatitis A, B, C or E virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus), autoimmune diseases (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) and metabolic and genetic diseases (hemochromatosis, α 1-antitrypsin deficiency, wilson's disease). Alcohol consumption needs to be documented thoroughly, ischemic hepatitis must be ruled out and liver imaging might be helpful for excluding other pathologies^[17,33]. None of the currently used causality assessment tools were developed specifically for herbal dietary supplements^[17]. The same diagnostic guidelines designed for idiosyncratic DILI apply to herbal products as well. The 2 most commonly used approaches are the roussel uclaf causality assessment method (RUCAM) and expert opinion process. The RUCAM calculates a total score assigning points to clinical and biochemical parameters; a higher score indicates increased likelihood of hepatic injury due to a specific medication^[34]. The RUCAM can be calculated only for a single drug each time and labelled toxicity is considered; these features are major restrictions in the use of RUCAM for proof of herbal medicine-related liver injury, since herbal preparations include multiple ingredients and hepatotoxicity warnings seldom appear in their labels. Expert opinion is being used by the drug induced liver injury network^[35] and it appears to render higher agreement rates^[36]. Novel causality assessment tools specific to herbal dietary supplements have been proposed and preliminary results appear promising^[37].

In conclusion, herbal medicine products represent a common therapeutic approach in the East and are gaining increasing popularity in Western countries. They are unjustifiably considered to be side-effect free; on the contrary, severe toxicity, including catastrophic hepatic injury has been reported in association with their use. Vigilance is required from both physicians and the general public. Physicians should always suspect herbal medicines when evaluating a patient with unexplained liver injury. Regulation standards for herbal products need to be reconsidered, so that the efficacy and safety of these products have been clearly demonstrated before they enter the markets.

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