

Liver Injury Induced by Herbal Complementary and Alternative Medicine

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KEYWORDS

• Regulatory • Herbal • Dietary supplements • Hepatotoxicity • Causality assessment

KEY POINTS

- Herbal and dietary supplements (HDSs) are being used with increasing frequency in American households. Several products and specific ingredients have been implicated in liver injury.
- The regulatory environment for HDSs is different than that for conventional medications; premarket testing for safety and efficacy is not required.
- The diagnosis of liver injury caused by an HDS is made as it is for drugs. However, the causality assessment process is confounded by the possibility of product adulteration and contamination, which may account for injury.
- Many different single herbal ingredients have been implicated in liver injury. However, multicomponent products are more likely to be implicated in liver injury, each with many ingredients making it difficult, if not impossible, to impugn any of them with certainty.

INTRODUCTION

Before the emergence of pharmacology as a science and the proliferation of the pharmaceutical industry that fueled the development of chemical and biologic medications, indigenous peoples who suffered illnesses or injuries depended on unconventional means of treatment, some now referred to as alternative medicine. A local healer was often consulted and might conduct animal sacrifice, perform incantations, or apply specific forms of scarification, whereas other approaches considered included prayer, massage, acupuncture, body manipulations, and especially the use of herbal medications. The use of herbal medications was particularly prevalent in the Far East,

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dating back centuries. The herbals used came from the leaves, stems, roots, seeds, and berries of local plants and also from the barks of trees. Thought to have potential medicinal properties, they differed by geographic location, local weather conditions, the available local plants, and by soil characteristics and the elevation at which the plant was grown.

The original use of herbals consisted of applying the plant or leaf directly to the injured or painful body part, or the administration by mouth of an extract of the plant or a concoction made from boiling the plant. Without knowing the medicinal component, what was thought to be helpful was far from pure and may have been contaminated. Nevertheless, for centuries, the traditional use of herbals consisted of administering what was thought to be a single herbal ingredient or a mix of a small number of individual ingredients thought to have a complementary effect when used together, selected and mixed by an herbalist with long experience. As scientific measures became available, the supposed principal medicinal ingredient could be isolated, facilitating access to these single-ingredient products. The next step in more recent times has been for commercial interests to become involved by developing products containing multiple individual herbal ingredients. These mixtures have generally consisted of 10 or more separate constituents, each ingredient thought to have its own medicinal effect, but without necessarily having the complementary effect thought to be important by the experienced herbalist. Although many such commercially created herbal products are sold in established health care stores, as many or even more are advertised and sold via the Internet.

At present, many peoples in third world countries use single-ingredient herbals to treat illnesses, in part because of custom but also because of the lack of availability and high cost of Western commercial drugs.¹ In Western countries, even though there is easy access to pharmaceutically developed drugs, there has been a growing interest in herbal and dietary supplements (HDSs) used either in conjunction with standard medications (complementary medicine) or on their own (alternative medicine). The reasons are multiple, including the high cost of many drugs, but additionally the unpleasant or even serious side effects from some drugs, the disillusionment with general medical care, the wish to take personal control of one's health, the effort to increase well-being, and the belief in the effectiveness of herbal remedies. Moreover, there is the conviction that herbals are safe, having been used for centuries, and that conventional medical providers may not be well informed about these remedies.² Unlike peoples in less developed countries, westernized individuals are more likely to use products containing multiple ingredients, purchased either in health care stores or from the Internet, which they trust as sources of information.³ Although early use focused largely on improving well-being, herbal products are now more commonly used for bodybuilding purposes and in the hope of promoting weight loss. Furthermore, they are used frequently to treat a wide variety of chronic diseases, including cancers, chronic pain, rheumatologic and cardiovascular diseases, diabetes, human immunodeficiency virus infection, and even liver diseases.⁴⁻⁶ This pattern of use has raised concern because they have sometimes supplanted clearly effective treatments using standard medications with supposed medications that are less likely or even unlikely to be effective. Interactions with standard medical therapies is an additional concern,⁷ the potential for which has recently been studied in patients being treated for cancer.⁸

EPIDEMIOLOGY

Interest in and the level of use of HDS products seem to have increased in most Western countries, particularly in the United States. One of the earliest rigorous efforts to

assess the frequency of use of herbals and vitamins in the United States took place in 1990 via a telephone survey.⁹ Thirty-four percent of respondents disclosed the use of one or another form of complementary or alternative medicine (CAM), 2.5% admitting to a focus on herbals. A similar survey by the same researchers conducted 7 years later found an increase both in overall CAM use to 42% and in the use of herbals to 12.1%.¹⁰ Data from the National Health and Nutrition Examination Surveys (NHANES) have been particularly revealing. Beginning with the NHANES I survey conducted between 1971 and 1974, when 23% of the studied population reported the use of vitamin supplements,¹¹ there has been a consistent increase in reported usage of HDS products in subsequent NHANES surveys,^{12,13} reaching a figure of 52% of all respondents in the NHANES IV survey conducted between 1999 and 2000.¹⁴ Similar increases have been identified in other national surveys, including the National Health Interview Survey (NHIS) involving the noninstitutionalized US civilian population, the frequency of admitted herbal use increasing from 9.6% to 19% in 2 successive surveys,^{15,16} and a US Food and Drug Administration (FDA)-sponsored health and dietary survey conducted in 2002 finding that 73% of the screened population used supplements, half of which were herbals.¹⁷

Another indicator of the growing interest in the use of CAM practices in the United States is the extent of commerce attributed to purchasing products or in payment to CAM practitioners. One survey estimated that, in 1990, \$14.6 million was spent on CAM therapies, increasing to an estimated \$27 million in 1997,¹⁰ whereas another analysis, conducted by the National Center for Complementary and Alternative Medicine, National Institutes of Health (NIH), concluded that the annual expenditure had increased to \$33.9 million in 2007.¹⁸ Most telling of all are data published by the American Botanical Council. This organization has been maintaining records of the estimated annual sales of herbs, noting that, in 1999, total sales were \$4110 million, increasing each year thereafter, with the exception of 2002 and 2003, to reach an expenditure of \$5200 million in 2010.¹⁹ Equally informative are the data from an ongoing study supported by the National Institute of Diabetes and Digestive and Kidney Diseases, NIH. The Drug-Induced Liver Injury Network (DILIN) Study involves 8 academic centers in the United States charged with identifying cases of liver injury from either conventional pharmaceutical drugs or from herbal products.²⁰ In a preliminary report of the DILIN's experience between 2003 and 2011, 679 cases of drug-induced liver injury (DILI) were enrolled, of which 109 (16%) were attributed to HDS products. This group accounted for the second most common class of agents causing drug-related hepatotoxicity. Most of these agents consisted of commercial mixtures. Moreover, the data show that there has been an increase over time of the proportion of HDS DILI cases relative to the total number of all identified cases of drug injury, conventional and HDS related.²¹

REGULATORY ENVIRONMENT

Perhaps the most common perception among the general public is that HDS products are safe and effective, which is presumably valid for vitamin supplements but may not be so for all herbal products. This perception may result from their accessibility, easy-to-read labeling, and effective marketing. However, the regulatory framework for natural products is different from that for conventional pharmaceuticals. The FDA has no authority to approve herbal products before marketing. Preclinical and clinical toxicologic testing, as well as early phase clinical trials to establish safety, tolerability, and efficacy, is not required for herbals.

The current regulatory framework for marketed HDS was put into place in 1994, through the Dietary Supplement Health and Education Act (DSHEA).²² Through this

act, dietary supplements were defined as products intended to supplement the diet, but not constitute a complete meal. A dietary supplement, by definition, contains one or more ingredients; these include vitamins, minerals, herbs or other botanicals, amino acids, or extracts thereof. According to this law, the product label must identify the contents through a complete listing of ingredients. In addition, a supplement label may not claim to diagnose, treat, cure, or prevent disease. The DSHEA prohibits regulation of herbal products by the FDA, leaving policing of efficacy and safety of these products to the manufacturers.

The next significant piece of legislation following the DSHEA of 1994 was the Final Rule for Dietary Supplement Current Good Manufacturing Practices, 2007.²³ This gives guidance to the industry on production standards, and compels manufacturers to provide assurance that their product is free from adulteration and contamination. Even with these two laws, adherence by manufacturers has been inconsistent.²⁴ The key responsibilities that these laws impart to the manufacturer and the FDA are listed in **Table 1**.

DIAGNOSIS OF HDS-INDUCED LIVER INJURY

The possibility that signs and symptoms of liver injury might be the consequences of HDSs requires thorough but diplomatic inquiry of the affected person as to whether an herbal or dietary supplement had been taken in the preceding months. However, patients often do not spontaneously divulge use of nonprescribed products to their providers, for a variety of reasons, including the concern that the questioning health care professional might disparage them for their use.^{2,25}

Diagnosing HDS-induced liver injury (HILI) requires a systematic analytical approach, as is done for liver injury from conventional drugs. A first step is to determine the latency of the injury, namely the time interval between the start of an agent and the onset of liver dysfunction, which is helpful in recognizing injury patterns characteristic of specific classes of drugs or HDS. However, this feature may have less

Regulation	Responsibilities	
	Manufacturer	FDA
DSHEA (1994)	Identify product ingredients and manufacturer on the label Provide disclaimer noting that product was not evaluated by the FDA for safety and efficacy, and is not intended to diagnose, treat, cure, or prevent disease	Defines supplements as vitamins, minerals, herbs, amino acids (and any concentrate, metabolite, extract thereof) Investigate allegations of attributable toxicity after marketing Conducts premarket review of safety data for new ingredients
cGMP (2007)	Must adhere to standards in identification, purity, strength, composition, and purity of the final dietary supplement Must evaluate the identity, purity, strength, and composition of dietary supplements	Supplements containing contaminants or not containing labeled ingredients are considered adulterated or misbranded

Abbreviation: cGMP, current good manufacturing practice.

value for implicating herbal products because their latency periods may be highly variable even in well-established instances of herbal hepatotoxicity. The quality or concentration of single-ingredient herbals may differ in the same product taken at different times depending on the geographic location, the growing conditions, or the extraction procedures used during its manufacture, as shown through several recently published examples.^{26–28} Multiingredient products may also have problems of inconsistency from batch to batch because of poor quality control during production. Therefore, HDSs marketed under the same label but purchased on different occasions and consumed over long periods of time may have to be regarded as potentially separate agents. Individuals under consideration for HILI should therefore always be questioned about their patterns of purchase of the implicated herbal product and especially whether there had been purchase of a new batch of the product in close proximity to the onset of injury.

The next helpful step to assess the possibility of HILI is to define the injury characteristics, namely whether it presents as hepatocellular, cholestatic, or a mixed pattern of injury. The injury pattern has been a useful diagnostic clue for hepatotoxicity from conventional drugs, as for example the typical hepatocellular presentation of injury caused by isoniazid.^{29,30} However, characteristic patterns of injury from HDS have been recognized for only a few products. Most notable is the presentation of liver injury from anabolic steroids, the core of bodybuilding supplements but sometimes unknowingly tainting other commercial products. Another instance is that of the pyrrolizidine alkaloids, present for example in Comfrey tea, which can lead to the development of the sinusoidal obstruction syndrome (previously, venoocclusive disease). These two examples are referred to again later in this article.

A third important step is to exclude all other causes of hepatic injury that can mimic hepatotoxicity, such as viral hepatitis, types A, B, C, and E; autoimmune and metabolic diseases; injury from coadministered conventional medications; alcohol injury; and hemodynamic insults. The approach is the same whether assessing possible liver injury from conventional drugs or HDSs. However, identifying the specific noxious ingredient in HDSs may be difficult or even impossible when the affected person is using a single herbal product that contains multiple ingredients, not all of which are identifiable, or is taking several different herbals concomitantly.

A fourth item that helps support a diagnosis of drug-induced or HDS-induced liver injury is that the biochemical abnormalities begin to subside after withdrawing the implicated agent; however, recovery from injury may be more prolonged than usually happens in recovery from acute viral hepatitis. Referred to as dechallenge, deceleration of injury can occur with variable rapidity. In some cases, the injury may progress to chronic liver disease and/or liver failure, an example being the evolution of pyrrolizidine alkaloid hepatotoxicity to the sinusoidal obstruction syndrome, as noted earlier.

In addition, the definitive indicator of DILI, whether from a conventional drug or herbal product, is that the injury subsides after discontinuing the drug but reappears when the implicated product is readministered. Even though an effective diagnostic maneuver, rechallenge is generally avoided because the recurrent liver injury may be more severe or even culminate in liver failure. The key steps in establishing an accurate diagnosis of HILI are listed in **Table 2**.

CAUSALITY ASSESSMENT IN HILI

Once clinical, biochemical, and serologic data have been gathered, methodical causality assessment must then be performed. Because there is presently no specific

Step 1	Ascertain a history of HDS as well as all medication use that preceded liver injury, and the duration of time from starting treatment to onset of liver injury (latency)
Step 2	Assign the pattern of injury as hepatocellular, cholestatic, or mixed
Step 3	Exclude other causes of liver injury
Step 4	Stop the implicated product and observe for improvement, or worsening on inadvertent readministration

biomarker for hepatotoxicity, linking a drug or herbal to identified liver disease has had to be based on one of several imperfect assessment approaches: the use of scoring systems, reliance on expert opinion assessment, or using probabilistic methods of analysis. Because of its limited applicability, probabilistic methods of analysis are not discussed in this article.

Scoring Systems

The Naranjo Adverse Drug Reaction Scale has been proposed for use in clinical trials,³¹ although not specifically for assessment of DILI. This system scores a reaction from -4 to $+13$ and is easy to use, but several elements limit its applicability outside the research trial setting. Its primary limitation is that the scoring is based on a placebo response. Also, information is required about drug concentration and dose relationship that is difficult to obtain in liver injury from HDS. Although it has been applied to assess causality for natural products,³² its value in this setting has been strongly questioned.^{33,34}

The most widely used scoring system is termed the Roussel Uclaf Causality Assessment Method (RUCAM).³⁵ Created in 1989, RUCAM permits scores ranging from 1 (unlikely to be drug toxicity) to 8 (highly likely to be drug toxicity). Although commonly used by industry, it is limited in its applicability to assessing causality in the setting of clinical trials. Moreover, its applicability in clinical practice, even though problematic regarding its value, is greater for injury caused by conventional drugs than for hepatotoxicity caused by HDS products. For example, one of the multiple items to be scored in the RUCAM system requires information on whether the label on the implicated product warns about potential liver injury, whereas another item that requires a score asks for past published experience of hepatotoxicity. Information on both these items is generally unavailable for most HDS products.

The Maria and Victorino Scale is a modification of the RUCAM scale and adds drug injury features that suggest an immune or immunoallergic response, namely fever, rash, arthralgia, eosinophilia, and cytopenias.³⁶ This scoring system has not been evaluated as a diagnostic tool for HDS-related hepatotoxicity.

Both of these causality assessment approaches have limited value with respect to HILI, largely because of the complexity of the involved products. As already noted, the components and their concentrations may vary in natural products that are harvested at different times of the year and in different locations; commercial products generally contain multiple ingredients and may have been unknowingly contaminated or deliberately adulterated. The Maria and Victorino and Naranjo scales ask for drug concentrations, but characterizing the chemical composition of HDS is a complex and costly task. Moreover, it may be difficult or even impossible to determine which of the many constituents is responsible for causing the liver injury, let alone identifying and implicating possible contaminants.

Assessment by Expert Opinion

Most published reports of hepatotoxicity are based on the evaluation of clinical, biochemical, and occasionally histologic features of the case but without using a uniformly established assessment process. The NIH DILIN Study Group therefore devised a graded scoring system to assess both the diagnostic likelihood of DILI and liver disease severity taking into account all the items described earlier that are required for complete causality assessment.²⁰ When first created, the scoring system was relevant only for liver injury caused by conventional drugs and not by HDSs. The DILIN scoring system brought uniformity to the process of causality assessment and has seemed to be more efficient in diagnosing DILI than the RUCAM method.³⁷ Its limitations for general application are that it used 3 independent expert reviewers, not generally available in clinical practice, and that the analytical approach remains subjective.

The DILIN Study Group recently worked to develop an expert opinion approach directed more specifically at HILI by incorporating elements that, *a priori*, have an impact on establishing a causal association between a liver injury event and a dietary supplement. These elements take into account the number of dietary supplements and the multiplicity of ingredients in a single product, the strength of the existing literature on the potential for hepatotoxicity of an implicated supplement, and the possibility that a concomitantly administered drug might have accounted for the presenting pattern of injury. In a small test-retest validation exercise, the developed procedure produced moderate agreement when assessed by 3 independent reviewers.³⁸ However, more work is needed to further improve this approach to causality assessment for potential HILI.

CONTAMINATION AND ADULTERATION

Because of the manner in which herbals are grown, they are at risk of contamination with potentially toxic chemicals. The original plant may be acquired from the wild or specifically cultivated for eventual medicinal use. In the latter situation, they are likely to have been sprayed with pesticides. They are then harvested, dried naturally or artificially, after which constituents are extracted using organic solvents or subjected to countercurrent extraction with supercritical gases, irradiation, or cold compression. Thereafter, they are stored and eventually packaged for distribution. In view of this protracted process, there is opportunity for contamination, which has been reported to involve microbials,^{39,40} mycotoxins,⁴¹ or heavy metals,^{42–48} which may account for the liver injury.

More disconcerting is that some manufacturers have deliberately adulterated the herbal mixture with pharmaceutical drugs without informing the consumer or listing them in the label. There are thus reports of the identification of the following drugs found in some herbal products: corticosteroids, sildenafil citrate, diclofenac, chlordiazepoxide, chlorpheniramine, diphenhydramine, hydrochlorothiazide, promethazine, triamterene, benzodiazepines, and antiinflammatory drugs.⁴⁹ Other drugs identified in the herbal product PC-SPES used to treat prostatic cancer included indomethacin, diethylstilbestrol, and warfarin,^{50–52} whereas a phosphodiesterase 5 inhibitor has been identified in a herbal product used to treat erectile dysfunction.⁵³ In addition to deluding the consumer into believing that the herbal product had a specific effect, whereas it was the added pharmaceutical drug of which they were unaware, it is conceivably one or other of these added products that might account for subsequent identified liver injury.

HDS COMMONLY ASSOCIATED WITH LIVER DISEASE

Through its experience in accruing cases of hepatotoxicity associated with drug and dietary supplements, the US DILIN offers a contemporary view of HILI. In particular,

the DILIN's preliminary findings indicate that supplements used for bodybuilding and weight loss purposes, categorized as such by a review of their marketing materials, constituted the most common of the HDS products accounting for HILI (Table 3).²¹ Furthermore, most of the implicated HDS products identified through the DILIN study consisted of multiingredient commercial mixtures. The discussion that follows regarding specific HDS products identified to have caused hepatotoxicity is therefore framed in the context of these findings. The reader is also referred to a recent comprehensive review of all published literature on HDSs implicated in liver injury.⁵⁴

SUPPLEMENTS USED FOR BODY AND MUSCLE BUILDING

Many products to promote building muscle mass are offered on the Internet, and most such products contain ingredients reminiscent of steroids. Whether these ingredients are true anabolic steroids or their derivatives or precursors is unclear. Regardless, the liver injury that results from them presents in a characteristic way.⁵⁵ The involved patient is typically a young man seeking to increase his muscle mass who has obtained information on the product by searching the Web; after a variable period of use, the patient develops prolonged jaundice and intense pruritus. The biochemical pattern of injury is generally a modest increase in aminotransferase levels and, early in the course, a variable increase of alkaline phosphatase levels, followed by a prolonged period, often lasting weeks to months, of hyperbilirubinemia. Complete recovery can be expected.

That anabolic steroids may cause several adverse effects including cholestasis, peliosis, or hepatic neoplasms, has long been known.⁵⁶ Despite declaring anabolic steroids as controlled substances in sporting circles because of their tendency to

Table 3
DILIN patients (n = 109) by type of HDS product

Type of HDS Products: Main Marketed Indications for Use	DILIN Patients with Suspected HILI; n (%)
Bodybuilding	36 (33)
Weight loss	28 (26)
Immune support	13 (12)
Cough/cold	12 (11)
Depression/anxiety/cognition	9 (8)
Multiple vitamins	8 (7)
Chinese herbs	7 (6)
Antiinflammatory/analgesic	6 (6)
Insomnia	4 (4)
Energy booster	4 (4)
Joint support	3 (3)
Gastrointestinal upset/diarrhea	3 (3)
Sexual performance	2 (2)
Chelation	2 (2)
Colon cleanser	2 (2)
Menopause	2 (2)
Miscellaneous	4 (4)

cause liver injury, liver disease continues to be reported among persons who use bodybuilding supplements⁵⁷⁻⁶¹ and is seemingly attributable to such steroids or their derivatives.

Examples of bodybuilding supplements identified to have caused liver disease include the products T Bomb II and Superdrol.^{57,58} Noteworthy, the clinical presentations in those who used these bodybuilding supplements were not always purely cholestatic because some presented with features of hepatocellular injury.

SUPPLEMENTS COMMONLY USED FOR WEIGHT LOSS

Conjugated Linoleic Acid

Used as a weight loss supplement, conjugated linoleic acid has been reported to cause hepatotoxicity.⁶² A recent report has described fulminant liver failure leading to transplantation.⁶³ Injury is suspected to be a result of lipid peroxidation.

Ephedra

Also known by its Chinese herbal name, ma huang, ephedra has been a common ingredient in weight loss supplements, exploited for its stimulant properties. However, removal of this ingredient from Hydroxycut products did not mitigate hepatotoxicity. Injury thought to be caused by ephedra presents as a hepatocellular pattern. Several reports of hepatotoxicity have been attributed to this product, with some instances leading to liver transplantation.⁶⁴⁻⁶⁸

Germander

Used as an antiinflammatory agent for many ailments, as well as for weight loss, this herbal product has been linked to hepatotoxicity and has even been removed from many European markets, stemming from multiple reports of attributable hepatotoxicity, mostly from France in the early 1990s. A hepatocellular pattern of injury has been reported, as well as a few fatalities.⁶⁹⁻⁷⁸

Green Tea (Camellia sinensis)

Consumed by many people around the world as a beverage, an extract of green tea (green tea extract [GTE]) is a common ingredient in many HDS products, especially those used for weight reduction. Catechins are polyphenolic compounds comprising approximately 10% GTE. These polyphenols are likely responsible for the antioxidant activity and other health benefits that have been attributed to GTE. However, GTE and at least one component, catechin (epigallocatechin-3-gallate), have been implicated through in vitro and in vivo studies as dose-dependent hepatotoxins.^{79,80}

There are numerous reports of hepatotoxicity from GTE and the US Pharmacopeia has undertaken a detailed review of the issue.³² The liver injury generally presents with a hepatocellular pattern and fatality caused by this product has been reported.⁸¹ Particularly convincing are reports indicating recurrence of the injury on reexposure.^{82,83}

Herbalife (Herbalife International Inc)

Another compilation of agents under a single label are the Herbalife products. Weight reduction is among the marketed purposes for use. Other uses include nutritional supplementation and promotion of overall well-being. Initial reports of liver injury from these products emerged from Israel and Switzerland.^{84,85} Since these initial reports, others have been published.^{40,86,87} Injury is predominantly hepatocellular in nature, with highly variable latencies.

Hydroxycut (Iovate Health Sciences Inc)

There are many products under the brand name Hydroxycut, most of which seem to be used for weight loss. The first case reports of liver injury resulting from Hydroxycut products occurred in 2005⁸⁸; there have subsequently been others, including one describing a fatal outcome.^{89–92} With this information, the FDA issued a warning and the manufacturer withdrew some of its products from the market.⁹³ The pattern of injury is predominantly hepatocellular, although some reports also described a protracted cholestatic course.

Usnic Acid

In vitro and in vivo evidence has shown the potential for usnic acid to cause cell injury and necrosis.^{94,95} As a weight loss supplement, it has been incorporated into other products recognized for their injurious potential, even leading to acute liver failure.^{65,96–98}

SUPPLEMENTS USED FOR JOINT HEALTH

Flavocoxid

Flavocoxid is a medical food with the unique feature of being a dietary supplement that is administered under the supervision of a physician, as with a conventional drug, but is not required to undergo the same rigorous premarket safety and efficacy testing.⁹⁹ Flavocoxid (Limbrel) seems to have antiinflammatory properties and is therefore used for relief of osteoarthritis symptoms.¹⁰⁰ In a recent case series report, the type of injury noted was of a mixed hepatocellular/cholestatic pattern, with some patients experiencing severe injury.¹⁰¹

Another product implicated in causing liver injury is Move Free Advanced (Schiff Nutrition Group Inc), a complex mixture of ingredients that includes Chinese skullcap and glucosamine.¹⁰²

SUPPLEMENTS COMMONLY USED TO TREAT GASTROINTESTINAL COMPLAINTS

Aloe Vera

Aside from its use as a topical emollient, aloe vera has been used to treat gastrointestinal symptoms. There are several reports of hepatocellular injury from the use of aloe vera but none that have culminated in death or liver transplantation.^{103–107}

Chaparral

Taken orally, chaparral has been used for digestive disorders such as cramps and bloating, but for other system complaints as well, such as pulmonary and respiratory disease, cancer, and infections. Most reports of chaparral-induced liver injury describe a predominantly hepatocellular pattern of injury occurring with a wide variation in latency, up to nearly a year after exposure.^{108,109} Although most cases resolved with cessation, the injury has been reported to require liver transplantation.^{66,110}

Greater Celandine (Chelidonium majus)

Greater celandine has been used in the past for various gastrointestinal ailments, and greater celandine hepatotoxicity has been reported to lead to a hepatocellular pattern of injury, although cholestasis has also been described.^{111–113} Injury usually appears within 3 months of use. No fatal cases have been reported.

SUPPLEMENTS COMMONLY USED FOR PAIN RELIEF***Black Cohosh***

Black cohosh is used to relieve menopausal symptoms. Several reports of hepatotoxicity attributed to this product have appeared in the literature, prompting a comprehensive review of the subject by the US Pharmacopeia,¹¹⁴ a review that has drawn criticism.³³ Affected patients are reported to develop liver disease ranging from asymptomatic increases in the aminotransferase levels to acute liver failure,^{115–122} and some patients have shown autoimmune features.^{123,124} Most commonly, the liver injury presents with a hepatocellular pattern.

Comfrey

Comfrey is most commonly used as an ingredient in oral supplements and topical applications for pain relief. Often brewed as a tea, liver injury has been reported to occur after several months of use, most commonly with the features of the sinusoidal obstruction syndrome.^{125–130} Patients typically develop severe liver injury characterized by right upper quadrant pain, hepatomegaly, and ascites. Increased levels of alkaline phosphatase are common and, over time, advancement to the development of posthepatic portal hypertension with ascites and, eventually, liver failure occurs. This presentation has been attributed to its component pyrrolizidine alkaloids, which create toxic intermediates that are injurious to sinusoidal endothelium, thus leading to the obstructive process.¹³¹ Comfrey has been banned in most countries.

SUPPLEMENTS COMMONLY USED FOR PSYCHOTROPIC EFFECTS***Kava Kava***

The active ingredients in kava preparations, thought to be responsible for its psychotropic properties, are the kavapyrones (kava lactones). Kava has traditionally been consumed as a ceremonial drink in the South Pacific, following simple aqueous extraction. Cases of liver injury in Western countries had been thought to be caused by the alcoholic and acetonetic extraction process, which yields a higher concentration of kava lactones.^{132–134} However, closer examination of cases suggests that the extraction process has little if any bearing on hepatotoxicity.¹³⁵

Following a series of reports of liver injury, some severe and leading to liver transplantation and death, kava products were banned from the market in several European countries,^{136–139} beginning in 2001 in the United Kingdom.¹⁴⁰ Some have challenged the literature on kava hepatotoxicity, suggesting inadequate causality assessment¹⁴¹ or the possibility that nonkava compounds taken simultaneously are the cause for injury.¹⁴² The case reports indicate a predominantly hepatocellular pattern of injury, with variable latency periods, suggesting an idiosyncratic mechanism of injury. Other mechanisms of injury have been considered but none have been proved.¹⁴³ Acute liver failure and transplantation have been reported as a result of kava toxicity.¹³⁹

Skullcap

The flavonoids that are contained in skullcap are thought to be responsible for its sedative effect. Injury tends to be hepatocellular. Attribution to skullcap has been questioned because most reported cases of hepatotoxicity seem to have been confounded by the use of other HDSs.^{102,115,144}

Valerian

Used to treat insomnia as well as other conditions, such as anxiety and digestive disorders, valerian has been implicated in cases of HILI.^{145,146} However, causality in most

cases was confounded by other HDSs taken concurrently. The pattern of injury is usually hepatocellular.

SUPPLEMENTS COMMONLY USED FOR MISCELLANEOUS PURPOSES

Noni

The fruit of the *Morinda citrifolia* plant yields noni juice, long used for a multitude of medical applications. Liver injury has been reported, occurring predominantly in a hepatocellular pattern, with resolution on cessation; confounding factors were present in some cases.^{147–152} Animal and human pharmacology studies have failed to provide supporting evidence of its hepatotoxicity.^{153,154}

Pennyroyal

Pennyroyal has been used as an insect repellent, abortifacient, and to induce menses. It is derived from the plant *Mentha pulegium*, and has long been known to be toxic, inducing seizures, circulatory collapse, and multiorgan failure, with symptom onset occurring within a few hours after exposure.^{155–158} The pattern of liver injury tends to be that of acute necrosis. The main constituents of pennyroyal, pulegone and menthofuran, are thought to induce hepatotoxicity in a manner similar to acetaminophen.¹⁵⁹

Traditional Remedies

Traditional remedies comprise Asian, Chinese, or ayurvedic products. The literature contains reports of liver injury attributed to various ingredients contained in traditional remedies.¹⁶⁰ These include ma huang, as previously described, *Atractylis gummifera*,^{161,162} Ba jiao lian,¹⁶³ dai-saiko-to,^{164–166} and jin bu huan.^{167–170} It is common for traditional remedies to be adulterated with conventional medications¹⁷¹ or heavy metals.⁴²

SUMMARY AND FUTURE DIRECTIONS

The evidence is convincing that there is extensive and even growing use of HDS products in Western countries, almost rivaling that of the use of conventional pharmaceutical drugs. Convincing also is that, contrary to popular belief, these products are no safer than prescription drugs and some may be more likely to cause harm. Past reports describing herbal hepatotoxicity focused largely on single herbal products, many used in their traditional settings, mostly but not exclusively in third world countries. What was not readily apparent was that, in westernized countries, especially the United States, the focus seems to have shifted to the use of herbals containing complex mixtures, many taken for specific reasons, mostly for bodybuilding or weight reduction purposes. This trend has become apparent from data collected in the NIH DILIN study, which enrolls all subjects identified with apparent drug-related liver injury, regardless of whether a conventional medication or a herbal product is involved. Among the enrolled cases of DILI in the DILIN database, only a few involve the single products that have been the focus of previous attention.

This finding raises the problem of needing to conduct causality assessment of products that include multiple ingredients, not all of which can be easily identified, making it difficult or even impossible to identify the component responsible for causing the liver injury. Added to this problem is the uncertainty of whether the toxic compound might be an unrecognized contaminant.

Future research must include expanding data collection of instances of HILI in real time in order to confirm and broaden knowledge of the potentially harmful effects of

herbal products. These data would allow better categorization of the injury patterns according to class or use, augment the ability to chemically isolate the individual known and unknown constituents, and provide the opportunity to improve the HDS-related causality assessment process.

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