Hepatotoxicity of Botanicals

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Abstract

The scale of the problem of hepatotoxicity of botanicals is reviewed. This problem was found to be very small, largely limited to idiosyncratic reactions (as opposed to intrinsic toxicity of herbal compounds for the liver), and hampered by the availability of high-quality evidence against intrinsic hepatotoxicity. Claims that herbal hepatotoxicity is common but hidden could not be substantiated. Various herbs sometimes considered hepatotoxic are reviewed in depth, including *Piper methysticum* (kava); *Larrea tridentata* (creosote bush); unsaturated pyrrolizidine alkaloid–containing herbs, such as *Symphytum officinale* (comfrey) and *Tussilago farfara* (coltsfoot); *Cimicifuga racemosa* (black cohosh); and *Camellia sinensis* (green tea) and its catechins.

Introduction

Many chemicals can cause hepatotoxicity. This is true of pharmaceuticals, industrial chemicals, and compounds in herbs.[1,2] Every year, many cases of toxic, idiosyncratic hepatitis occur for which no specific cause can be determined. There is concern from some parts of the conventional medicine community that a higher portion of these cases than was previously suspected is the result of previously unidentified herbal hepatotoxins or to known potential hepatotoxins that have not been tracked.

For example, one retrospective analysis of all 20 patients referred for liver transplantation at one Veterans Administration hospital in Portland, Oregon, found that 7 patients (35%) had no other explanation for liver failure (and these patients underwent extensive investigations) other than ingestion of herbs previously reported to cause hepatotoxicity.[3] Three (15%) additional patients were taking known hepatotoxic herbs but also had some other plausible explanations for their liver failures (such as hepatitis B in 2 cases). As a result, in this small sample, herbs were the single largest cause of hepatic failure. Drugs were a very close second, with 5 patients (25%) having acetaminophen-induced hepatotoxicity and 1 patient (5%) having disulfiram toxicity (including 1 of the patients who was taking hepatotoxic herbs together with disulfiram).

However, this top placement of herbs as the cause of liver failure was based on there being just 1 more patient who had a possibly herb-related problem versus a drug-related problem (7 versus 6 patients with problems caused by herbs versus drugs)—a difference that was as easily explained by chance as by the existence of an epidemic of herbal hepatotoxicity.[3] The authors of this study urged stricter regulation of these herbs despite some important questions that remained unanswered, such as the scope of the problem. For instance, how many users of the herbs had the most extreme negative outcome versus total number of users of the involved herbs?

Another study looked at 45 patients with chronic hepatitis B who were hospitalized because of liver dysfunction. These patients were admitted to one hospital in Hong Kong and screened prospectively for use of Chinese herbal medicines.[4] Seven patients (15.6%) were found to be taking Chinese herbal medicines that appeared to explain their liver dysfunctions. Four of these patients had severe outcomes (death, liver transplantation, or accelerated cirrhosis probably requiring transplantation). Again, there was no attempt to assess the scale of the problem in the total population (e.g., how many people with hepatitis B who took herbs had extreme negative outcomes? Or, how many people who took herbs did not have such reactions?).

At the 2013 Liver Meeting of the American Association for the Study of Liver Diseases, Victor Navarro and associates presented information from the National Institute of Diabetes and Digestive and Kidney Disease's Drug-Induced Liver Injury Network at 10 sites, most of which were in the Northeastern United States.[5] Between 2003 and 2013, the network judged that, of 1035 patients, 845 had liver disease probably, very likely, or definitely caused by drugs or dietary supplements. Of these cases, 136 (16%) were related to problems with dietary supplements (some problems—but not all—were caused by herbs), and 45 of the 136 (35%) cases

Criteria for Proof of Intrinsic Hepatotoxicity of an Herb

1. Multiple case studies of clinical liver disease in humans exposed to the herb
2. Clear dose–response curve
3. Specific extracts containing specific constituents that repeatedly cause liver damage (in human case reports and in animal models mirroring human responses at common doses)
4. Identical or a very similar pattern of liver pathology in all reported cases
5. At least 1 human case study in which reexposure resulted in repeated signs of liver damage (obviously may not exist for ethical reasons, but sometimes patients do reexpose themselves)

were related to body-building supplements. The number of dietary supplement–related hepatotoxicity cases rose during the study period.

This study[5] did not compare the number of cases with problems to the number of users of dietary supplements and did not validate the ingredients of any of the implicated dietary supplements. In addition, the study conflated body-building supplements with many other types of supplements without strong histories of adulteration. Many body-building supplements are notorious for adulteration with many different kinds of conventional pharmaceuticals and have, in many cases, been adulterated with steroids.[6] This study did not have a design methodology to ensure that all patients with drug-induced liver injuries were included. In addition, as might be expected, the study showed that pharmaceutical-associated liver disease was far more common than that caused by supplements.

The current authors posit that, despite concerns raised in the conventional literature, there is no increase in herbal hepatotoxicity out of proportion to their use, there is no "hidden epidemic" of herbal hepatotoxicity, and that the existing regulatory framework has effectively eliminated the few very serious problematic herbs from the marketplace (along with a few essentially "innocent bystanders"). Much of the purported herb-induced hepatotoxicity appears in poor-quality case studies that fail to provide any analysis of the product(s) involved and thus fail to: (1) rule out adulteration and contamination; (2) provide important information about patients that might suggest alternative causes of liver disease; and (3) use existing tools for assessing causality.[7]

With respect to early reports of problems, there has been a lack of systematic investigation by any industry or government body, resulting in scattered and sometimes conflicting outcomes. Most arguments for a "hidden epidemic" fail to note that the number of cases is not actually rising at a similar pace as the rapid rate of increased use of natural products. Instead, these arguments rely on case studies and other flawed evidence for the supposed epidemic and confuse adulteration with intrinsic herbal hepatotoxicity.[8]

Hallmarks of Idiosyncratic Herbal Hepatotoxicity

1. No clear dose–response curve
2. Highly distinct extracts of the same herb are all associated with hepatotoxic reactions
3. No constituent(s) can be identified that induce hepatotoxicity reliably in animal models or humans
4. Variable patterns of liver pathology in reported cases

In addition, with great frequency, many published reports of herbal hepatotoxicity could equally be attributable to other causes.[9] In addition, many confirmed liver failure cases actually involve idiosyncratic reactions to herbs as opposed to intrinsic hepatotoxicity (Criteria for Proof of Intrinsic Hepatotoxicity of an Herb and Hallmarks of Idiosyncratic Herbal Hepatoxicity clarify this important distinction further). Several examples of supposedly problematic herbs are discussed to illustrate and support the positions of the current authors.

Kava

Piper methysticum (kava) is a shrub native to the Pacific Islands; its root is a well-known and popular anxiolytic. A few cases of hepatotoxicity related to kava preparations and constituents began to appear in the 1990s. By 1996, the German government mandated labeling for acetone extracts of kava warning of possible hepatotoxicity, and in 1997, the American Herbal Products Association required its members to label their kava products as potentially hepatotoxic. In the early 2000s, European governments began to restrict or ban sale of kava products, followed eventually by Canada and Australia. Kava has not been banned in the United States. Many of the bans were based on very small numbers (< 100) of case studies reported globally, most of which lacked even the most basic information to assess a causal connection between kava and hepatotoxicity.[10]

In one analysis of 76 cases of purported kava hepatotoxicity reported worldwide, only four reports could show an absolute connection with kava as the cause and twenty-two showed a possible connection. The remaining reports either had minimal evidence of causes, lacked enough information to make any reasonable statements about causation, or were duplicate reports.[11]

A detailed analysis of 26 cases reported to the German drug regulatory authorities showed that most of these cases could not be connected with kava and that some cases originally deemed "probably" caused by kava were based on very dubious analyses.[12] As an example, one such "probable" case involved a 33-year-old woman who overdosed on ethanol (a known hepatotoxin), acetaminophen (another known hepatotoxin), and other analgesics, and was shown to be genetically CYP2D6-deficient (which may have impaired her ability to detoxify kava and other

Table 1. *Larrea tridentata* and NDGA as a Tissue Protector

Model	Benefit	Reference
Mouse bone marrow	NDGA protected against oxidative genotoxicity	Siddique, et al., 2008[a]
Rats	NDGA protected against cisplatin-induced acute renal injury	Lee, et al., 2009[b]
Rats	NDGA protected against chemically-induced nephrotic syndrome	Lee, et al., 2009[c]
Rats	NDGA protected against fatty liver caused by a high-fat diet	Lee, et al., 2010[d]
Rats	NDGA ameliorated fatty liver in rats genetically prone to this condition	Zhang, et al., 2013[e]

[a]Siddique YH, Ara G, Beg T, Afzal M. Antigenotoxic effect of nordihydroguaiaretic acid against chlormadinone acetate–induced genotoxicity in mice bone-marrow cells. J Nat Med 2008;62:52–56; [b]Lee DW, Kwak IS, Lee SB, et al. Post-treatment effects of erythropoietin and nordihydroguaiaretic acid on recovery from cisplatin-induced acute renal failure in the rat. J Korean Med Sci 2009;24(suppl):S170–S175; [c]Lee DW, Kwak IS, Lee SB, et al. Effects of celecoxib and nordihydroguaiaretic acid on puromycin aminonucleoside-induced nephrosis in the rat. J Korean Med Sci 2009;24(suppl):S183–S188; [d]Lee MS, Kim D, Jo K, Hwang JK. Nordihydroguaiaretic acid protects against high-fat diet-induced fatty liver by activating AMP-activated protein kinase in obese mice. Biochem Biophys Res Commun 2010;401:92–97; [e]Zhang H, Shen WJ, Cortez Y, et al. Nordihydroguaiaretic acid improves metabolic dysregulation and aberrant hepatic lipid metabolism in mice by both PPARα-dependent and -independent pathways. Am J Physiol Gastrointest Liver Physiol 2013;304:G72–G86.

NDGA, nordihydroguaiaretic acid.

compounds she ingested). These many complicating factors did not rule out that her kava exposure *may* have played some role in her liver failure, but they certainly made it impossible to implicate kava as the definitive problem.

Reports of kava hepatotoxicity cases then mostly ceased. While this would be expected in places where it was banned, there was also a dearth of cases reported in the United States where kava was still sold widely. Although some kava constituents, such as pipermethystine and flavokavain B are cytotoxic in vitro, no animal studies or well-designed animal models that matched human conditions have confirmed any compound in kava to be consistently hepatotoxic.[13] Some researchers have posited that leaves or stem peelings were problematic in low-quality extracts, although, in one in vitro study, these parts of the plant were less toxic to hepatocytes than root extracts.[14] Even long-term, high-dose studies have not been able to show that kava extracts decrease survival rates or cause clinical liver disease in rodents, despite some histologic evidence of *some* hepatic damage.[15]

Whether aflatoxins or other mycotoxins contaminating kava grown in the hot, humid conditions of the South Pacific may be implicated has still not been resolved.[16] Aqueous, ethanol, and acetone extracts have all been associated with human cases of hepatotoxicity, although they have very distinct constituent profiles.[17] The absence of a clearly defined toxic component in kava, the lack of a clear dose–response curve, and the lack of ability to replicate toxicity of kava extracts in animal models all argue for the substantiated reports of kava hepatotoxicity having been idiosyncratic in nature. This means that there may be some individuals susceptible to toxicity at any dose, and that it will not harm the vast majority of people who are non-susceptible.[18] It is thus highly illogical to ban kava because of rare reports of idiosyncratic reactions to it, given their rarity and the fact that many other substances also cause idiosyncratic hepatotoxicity on a similar scale.[19]

Shedding Light on the Kava Controversy

Teschke et al. explained some of the complex factors involved in trying to determine whether or not *Piper methysticum* (kava) was hepatotoxic:

> Unfortunately, we missed the chance to analyze in time the kava products taken by the few patients with toxic liver diseases connected with a probable or highly probable causality for kava, which leaves us with retrospective speculations and assumptions. In particular, there was never any analysis regarding the used kava variety (including kavalactone specifications for noble, medicinal, Two-Day, or wild varieties), plant parts, adulterants, impurities, pipermethystine, flavokavain B, and mold hepatotoxins in any of the consumed kava products that caused hepatotoxicity in the few individuals.[18]

Creosote Bush

Larrea tridentata (creosote bush) is frequently referred to as chaparral. The creosote painted on telephone poles to prevent rotting is derived from petrochemicals but does smell like this plant. This long-lived shrub is often considered the most important medicine among indigenous peoples of the Sonoran desert, where the shrub is the indicator species.[20]

A series of case reports of hepatotoxicity associated with creosote bush appeared in the 1980s and 1990s.[21] Approximately 25 total cases have been reported in the literature up to the main publication, Sheikh, et al.'s 13 cases published in 1997.[22] Only 2 other cases appear to have been reported since then: 1 with multiple complicating factors suggesting at most that creosote bush may have aggravated underlying liver disease,[23] and 1 in which the patient had a 15-year history of taking creosote bush and kava with a surprisingly mild liver pathology ("patchy necrosis and mild lymphoid infiltrate") who died of multiorgan failure.[3] And even if there is substantial underreporting of cases, the number of cases is still extremely low, compared to the number of people exposed to the herb (which, extrapolating from published data, is maybe a few hundred people globally becoming ill from all herbs among hundreds of millions of total users; for creosote bush, it is perhaps 50 of several million users).

Table 2. Medicinal Plant Sources of Unsaturated Pyrrolizidine Alkaloids

Family	Species	Common name
Boraginaceae	*Borago officinalis*	Borage
	Symphytum spp.	Comfrey
	Cynoglossum officinale	Hound's tongue
	Pulmonaria lobaria	Lungwort
	Lithospermum spp.	Gromwell
Asteraceae	*Tussilago farfara*	Coltsfoot
	Petasites spp.	Butterbur
	Senecio spp.	Birthwort
	Eupatorium cannabinum	Hemp agrimony

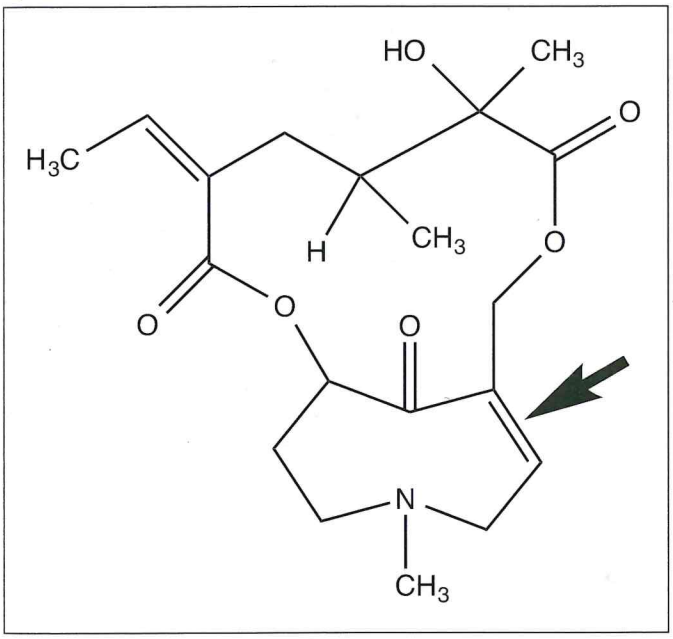


Figure 1. Senkirkine, an example of an unsaturated pyrrolizidine alkaloid. The double bond that makes this unsaturated is indicated with the large arrow.

At least one published study shows no hepatotoxicity. This was a small retrospective case series of 13 patients who took creosote bush tinctures internally for several months without clinical signs of liver disease.[24] Four patients with before-and-after laboratory results showed no elevation of serum transaminases in this study. Creosote bush was never formally banned in any jurisdiction according to the knowledge of the current authors.

One severely flawed meta-analysis claimed to support the hepatotoxicity of creosote bush by stating that the number of "hits" in the PubMed database (defined extremely vaguely as "identified database cases") associated with the undefined biochemical parameter "hepatotoxicity" was statistically significant.[25] The lack of any listing of the supposed "hits" (and thus an inability to analyze if they actually supported the purported link), the lack of definition of "hepatotoxicity," and the apparent inability of this model to include reports that showed an absence of hepatotoxicity (in essence, an "anti-hit") led to the conclusion that this was a low-quality article, with insufficient evidence to support the claims.

The fact that this article[25] was published in a peer-reviewed journal and is listed in PubMed means that it is likely to be cited and be used as support for claims that *L. tridentata* is dangerous, although even the most superficial analysis of this article shows it to be so deeply methodologically flawed as to be of no practical use. It is difficult to imagine that an article criticizing a drug using a similar approach would ever be published in a peer-reviewed journal.

The current authors posit that the available evidence at most shows that there may be a few cases of idiosyncratic reactions to creosote bush. However, the evidence is scant, so even this conclusion is weak. Once again, there is no established dose–response curve, no established toxic constituent that repeatedly causes hepatotoxicity, and no established animal model showing repeatable clinical hepatotoxicity. There are also multiple extremely different extracts (teas, capsules, and tinctures) associated with toxicity cases, and many human cases showing that creosote bush can be used safely.

One mouse study found evidence of a dose-dependent hepatotoxicity of nordihydroguaiaretic acid (NDGA; a major constituent in creosote bush) administered by intraperitoneal injection, but this does not pertain to the oral use of the complex plant.[26] There is scant other evidence of NDGA hepatotoxicity (and substantial evidence that this constituent is protective of various organs and is antitoxic; see Table 1), although, in rat hepatic microsomes, there is some evidence that NDGA may be converted to a quinone radical that could be damaging to cells.[27] Even this quinone, however, may actually be a beneficial metabolite similar to the lignans found in *Schisandra chinensis* (schisandra).[28] In the enormous dose of 2000 mg for 3 months, NDGA caused 1 patient with prostate cancer, of 12 patients in a study, to develop elevated serum transaminases.[29] For now, creosote bush remains a viable and safe medicine when it is prescribed by experienced natural medicine practitioners and herbalists at appropriate doses.

Table 3. Reports of Lack of Hepatotoxicity of Selected Major Medicinal Herbs

Herb (common name) & part	Model	Reference
Morinda citrifolia (noni) fruit	Rodents, humans	Potterat & Hamburger, 2007[a]
Pelargonium sidoides (umckaloabo) herb	Humans	Teschke, et al., 2012[b]
Rheum palmatum (rhubarb) root	Rats	Wang, et al., 2009[c]
Serenoa repens (saw palmetto) fruit	Rats	Singh, et al., 2007[d]

[a]Potterat O, Hamburger M. *Morinda citrifolia* (noni) fruit—phytochemistry, pharmacology, safety. Planta Med 2007;73:191–199; [b]Teschke R, Frenzel C, Wolff A, et al. Initially purported hepatotoxicity by *Pelargonium sidoides*: The dilemma of pharmacovigilance and proposals for improvement. Ann Hepatol 2012;11:500–512; [c]Wang J, Zhao Y, Xiao X, et al. Assessment of the renal protection and hepatotoxicity of rhubarb extract in rats. J Ethnopharmacol 2009;124:18–25; [d]Singh YN, Devkota AK, Sneeden DC, et al. Hepatotoxicity potential of saw palmetto (*Serenoa repens*) in rats. Phytomedicine 2007;14:204–208.

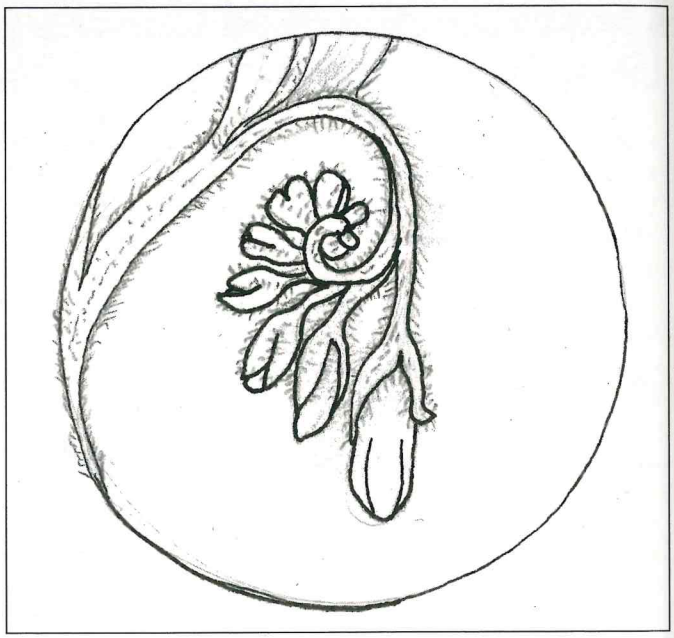
Unsaturated Pyrrolizidine Alkaloid–Containing Herbs

Many herbs contain compounds known as unsaturated pyrrolizidine alkaloids (UPAs). Essentially all members of the Boraginaceae family, some members of the Asteraceae family (see Table 2), and a few nonmedicinal members of the Fabaceae family contain these intrinsically hepatotoxic compounds. It is important to note that saturated pyrrolizidine alkaloids (SPAs), which are ubiquitous in the Asteraceae family, are *not* hepatotoxic. The difference between these two types of pyrrolizidine alkaloids is a single double bond that makes all the difference (see Fig. 1). The failure to distinguish between these alkaloids has led to false accusations of hepatotoxicity concerning herbs, such as *Echinacea* spp. (purple coneflower) and other members of the Asteraceae family, which contain SPAs but not UPAs.[30]

UPAs are metabolized in the liver by cytochrome P450 molecules to intermediates known as pyrroles, which are highly toxic; SPAs do not undergo such metabolic activation.[31] UPAs and SPAs exist in their main forms as well as in water-soluble forms known as *N*-oxides preformed in plants, and these forms also interconvert in the liver.[32] *N*-oxides can be viewed as relatively safe as they are excreted fairly easily, but they can also be converted back to UPAs and then into pyrroles and contribute to toxicity (while SPA *N*-oxides do not seem to undergo such back conversion to any significant degree).

Failure to account for preformed *N*-oxides in some studies may seriously underrepresent the potential hazard of high-UPA plants.[33] Pyrroles of UPAs form adducts with proteins and DNA in hepatocytes as well as in kidney epithelial cells, causing cell death in some and malignant transformation in others. The toxicity of UPAs is cumulative in that, once cell death occurs the cells are usually replaced by fibrotic tissue (and thus no regeneration of healthy cells is possible), and also because induction of cancer can ultimately result in death to the host.

However, not all UPAs are equally toxic. The efficiency with which they are converted to pyrroles, the efficiency of detoxification pathways, the efficiency of formation and elimination of *N*-oxides, and the degree of water solubility (and hence, ease of renal elimination) all contribute to determining whether or not a particular alkaloid will be harmful.[32] Many of these factors are dependent on the host's unique biology; this helps explain studies that clearly show some long-time users of UPA-rich plants having no definable toxicity.[34]



***Symphytum officinale* (comfrey). Drawing © 2014 by Kathy Abascal, BS, JD, RH (AHG).**

Other issues that may affect toxicity of UPA-containing medicinal plants include:

- Long-term breeding to decrease their toxicity (as is likely with *Symphytum officinale* [comfrey])
- Species misidentification and adulteration (e.g., *Petasites* spp. being sold as *Tussilago farfara*, both referred to as coltsfoot by some people,[35] and among different species of *Symphytum*[36])
- Differences in UPA levels in plant parts (e.g., *Symphytum* roots contain 10–100 times more UPAs than the leaves[37])
- Differences in plant part ages (e.g., young *Symphytum* leaves contain 16 times more UPA than mature leaves[38])
- Differences in extraction methods (typical infusions extract only one-third of the UPAs in the intact plant of *Symphytum*,[39] although, if *N*-oxides are also counted, the toxicity potential can be significantly higher[40]).

Epidemic outbreaks of UPA toxicity caused by food staples being inadvertently contaminated with UPA-rich herbs have been noted periodically.[41] In addition, honey can become contaminated with UPA if bees collect pollen from high-UPA plants.[42] In contrast, very little (0.1%) of UPAs eaten by cows passes into their milk, making this a highly unlikely source of indirect UPA poisoning.[43] Case studies of medicinal plants with UPAs causing harm in humans are generally of poor quality and fail to assess the purported causative agent(s) for adulteration or contamination, rarely have a clear dose determined, and often understate or fail to assess for concomitant risks such as preexisting liver disease or concomitant use of hepatotoxic drugs.[44,45]

Honey can become contaminated with UPA if bees collect pollen from high-UPA plants.

One relatively well-performed case series involved 4 Chinese women who were all exposed to a complex herbal tea containing UPAs.[46] While the problematic species in the tea was never identified, the level of UPAs and *N*-oxides present in the tea was carefully determined, and it was found that a 15 mg/kg total cumulative dose did not cause clinical disease, but severe clinical hepatotoxicity occurred at an 18 mg/kg total cumulative dose. The average daily intake of UPAs and *N*-oxides in these women was 30 mg.

With these complexities, it is clear that simple exposure to UPAs will not automatically result in hepatotoxicity or other toxicity. However, this is not a case of idiosyncratic liver toxicity, as there is a dose–response toxicity in many exposed people and animals that can be demonstrated repeatedly. Most use of UPA-containing medicinal herbs has been at lower doses for shorter periods of time, which may explain why historical reports of toxicity are lacking. Alternatively, this lack of evidence may be the result of underreporting and failure to correlate the herb(s) in use with the toxicity noted.

UPA-containing herbs should generally be avoided for long-term internal use, during pregnancy and lactation, and by people with concomitant liver and/or kidney disease. Topical use is generally safe and many studies of *Symphytum* show it to be effective for treating ankle sprains and promoting wound healing.[47,48] Short-term use of extracts with very low UPAs is acceptable in generally healthy patients, particularly with *Symphytum officinale*, which has proven to be one of the most effective herbs for healing peptic ulcers.[49] Extracts tested and shown to be UPA-free can be used long-term safely, such as *Petasites* extracts for migraines and allergies.[50] If UPA-containing extracts are used, concomitant use of *Glycyrrhiza glabra* (licorice) root or its constituent glycyrrhizin, *Panax ginseng* (Asian ginseng), or simple grape juice may help reduce these extracts' toxicities according to animal research.[51–53]

Black Cohosh

Cimicifuga racemosa (black cohosh) is a subshrub native to the deciduous forests of eastern North America. It is widely used as a reproductive aid, particularly to alleviate negative symptoms of menopause, as well as for providing relief for patients with arthritis and other conditions. Case reports of hepatotoxicity began to emerge in the early 2000s; these reports were ultimately substantiated in only 5 cases requiring liver transplantation.[54] An exhaustive meta-analysis reviewing the many clinical trials of black cohosh extracts for menopausal symptoms found no evidence of hepatotoxicity.[55]

The Dietary Supplement Information Expert Committee of the U.S. Pharmacopeia reviewed 30 nonduplicate cases of suspected black cohosh hepatotoxicity and concluded that all of them were possibly associated with the herb but none were definitively or probably associated.[56] In 69 cases (11 published and 58 reported to regulatory agencies), poor quality of evidence, inconsistencies in reported data for patients, lack of verification of the black cohosh products, lack of evaluation of concomitant risk factors for hepatotoxicity, and many other problems were noted, making an attribution of hepatotoxicity for black cohosh very difficult at best.[57]

Currently, black cohosh could only be said to be very rarely associated with idiosyncratic hepatotoxicity, and even that is based on very scant evidence of poor quality. Black cohosh simply has not been shown to be intrinsically hepatotoxic.[58]

One report from Canada suggested that adulteration of *C. racemosa* with different Chinese or North American species may have contributed to some cases of human hepatotoxicity.[59] Adulteration not associated with hepatotoxicity continues to be reported for products on the market.[60] Whether or not adulteration explains some or all cases of black cohosh–associated hepatic injury, and whether or not other species in the genus are hepatotoxic, remains to be determined.

Green Tea and Catechins

Catechins are a subtype of flavonoid and are particularly rich in *Camellia sinensis* (green tea), but they are also found in substantial quantities in raw chocolate and many other plants. A catechin, in isolation at doses as high as 3 g per day, was used in several trials for alcoholic and viral hepatitis in the 1980s with mixed results, but no obvious signs of hepatotoxicity.[61,62] Cases of hepatotoxicity associated with green tea began to appear in the 2000s, although they were exceedingly few, given the enormous levels of intake of green tea worldwide, thus showing signs of idiosyncratic toxicity rather than intrinsic toxicity.[63]

Extremely high doses (and thus probably clinically irrelevant for humans) of epigallocatechin gallate (EGCG), a common catechin in green tea, are hepatotoxic in mice, and this compound is cited as the hepatotoxic agent in green tea by many reports.[64] An analysis of 97 cases of suspected herbal hepatotoxicity concluded that many products con-

tain undisclosed catechins but that these are not correlated to hepatotoxicity.[65]

Counterbalancing these concerns are many reports of a hepatoprotective effect of catechins, green tea extracts, and green tea.[66,67] One large epidemiologic study found regular intake of green tea to be protective against elevated serum transaminases.[68] It should be noted that green tea extracts in capsules can contain levels of various catechins far above what could reasonably be obtained by drinking green tea, and thus may represent a threat not posed by traditional tea preparations (infusions) of the plant.

The case for green tea being hepatotoxic has not been made. Green tea extracts should be used somewhat more cautiously, as they can provide higher doses of single compounds that might be a problem, but even this is still highly speculative.

Conclusion

Many sensational case studies of hepatotoxicity associated with a range of herbs have been published. A handful of the purportedly hepatotoxic herbs involved in these cases has been reviewed in this article. Most of the research discussed here supports the case that herbs can be associated with idiosyncratic liver toxicity but that there are very few situations in which the intrinsic hepatotoxicity of herbs have been shown.

UPA-containing herbs are one example of intrinsically hepatotoxic herbs that must be used with caution—and only ever under careful supervision of a clinician knowledgeable about the intricacies of their safe use. Most herbs that are supposedly hepatotoxic—even some that have been banned (such as kava) in some countries—are not, and should not be avoided because of fear.

There is always a rare risk of idiosyncratic hepatotoxicity with any herb, medication, or chemical, and this cannot be the basis for restriction of use of these substances. Only those herbs with proven, consistent track records of problematic activity should be considered for regulatory control. A handful of case studies suggesting harm (particularly when there are no deaths, or very few deaths) should not be the basis for limiting the availability of herbs; these studies should only trigger further systematic investigations. This is particularly true when an herb is very widely consumed; a few cases of harm are inevitable in this instance because of idiosyncratic reactions alone. Idiosyncratic hepatotoxicity is not an appropriate basis for limiting the availability of a food, a medicinal herb, or a prescription drug.

At present, evidence of herbal hepatotoxicity is mostly of poor quality and quite scant, despite overreactions in the media and by a few ill-informed conventional practitioners. Greater effort needs to go into proactively determining which herbs are hepatotoxic and which are safe (see Table 3 for examples). We should take greater note of the many herbs that are hepatoprotective—those that could be used to improve the safety of a variety of hepatotoxic drugs.[69–71] ■

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