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REVIEW

Hepatotoxic slimming aids and other herbal hepatotoxins

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complementary and alternative medicine, drug-induced liver injury, herbal remedies, phytotherapy, terpenoids and health, traditional Chinese medicine, weight reduction.

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Abstract

Perceptions of safety and/or cultural mores prompt individuals to seek herbal slimming aids in preference to conventional dietary, physical activity and medication-based protocols. In recent years, terpenoid-containing dietary supplements have been implicated in causing severe and sometimes fatal hepatotoxicity. *Teucrium polium* (germander) was the first of these herbal products to be clearly linked to cases of acute liver failure. Subsequently, similar hepatotoxicity has been observed with other members of the *Teucrium* genus. While diterpenoid-derived reactive metabolites are central to germander hepatotoxicity, it may also be that the hepatic effects of compounds such as Sho-saiko-to, *Centella asiatica* and Black cohosh are linked to their triterpenoid content. Other non-terpenoid-containing herbal remedies marketed for weight reduction have been causally associated with significant liver injury. Important among these are preparations containing *N*-nitrosofenfluramine, usnic acid and ephedra alkaloids. Finally, we review recent data on known and emerging hepatotoxins such as Boh-Gol-Zhee, Kava, pyrrolizidine alkaloids and Shou-Wu-Pian. Better public and physician awareness through health education, early recognition and management of herbal toxicity and tighter regulation of complementary/alternative medicine systems are required to minimize the dangers of herbal product use.

Introduction

As the global pandemic of obesity unfolds, non-conventional methods of weight reduction are increasingly sought after. Herbal remedies continue to be a popular choice because of their perceived safety, easy availability, 'new age' living trends and other sociocultural influences including the desire to take 'organic' (complementary and alternative medicine, CAM). However, their safety aspects have been increasingly questioned by published reports of serious systemic, as well as hepatic, adverse effects.[1–8]

In the 7 years since herbal hepatotoxicity was reviewed in the Journal,[7] the hepatotoxic potential of herbal slimming aids has been repeatedly highlighted in numerous reports (Table 1).[9–11] In the present update article, the focus is on liver injury associated with such products as well as with other emerging hepatotoxic herbal remedies.

Methods

We searched MEDLINE, COCHRANE, OVID, POISONDEX and MICROMEDEX databases (2000–2007) for articles published in the English language using the key words 'complementary and alternative medicine', 'herbal remedies', 'traditional Chinese medicine (TCM)', 'phytotherapy' and 'toxic hepatitis'.

Results

Herbal slimming aids

N-nitrosofenfluramine

The hazards of poorly supervised weight-reduction strategies are well documented. Fenfluramine, a popular slimming aid in the early 1980s, was withdrawn due to its cardiac (valvular) toxicity. Fenfluramine is not hepatotoxic. However, a related compound *N*-nitrosofenfluramine, a constituent of two Japanese herbal products (Chaso or Onshido) has been implicated in cases of acute hepatitis.[11] The majority of those affected (10 of 12) have been women, aged between 25 and 63 years, who developed symptoms within 1–6 weeks of drug ingestion. Most patients recovered within 2 months. However, severe liver injury can occur. Two patients developed acute liver failure; one survived after a liver transplant, and the other died 6 weeks after admission. Liver explants showed massive hepatic necrosis or submassive necrosis and bridging fibrosis.[11]

Studies of *N*-nitrosofenfluramine-induced cytotoxicity in isolated rat hepatocytes demonstrate induction of mitochondrial permeability transition and uncoupling of oxidative phosphorylation.[12,13] The inevitable consequences of these cellular effects are intracellular ATP depletion and cell death.[12,13]

Table 1 Herbal slimming aids implicated in herbal hepatotoxicity

Herbal remedy	Toxic constituent	Pattern of liver injury	References
Chaso; Onshido; Sennomotokounou	*N*-nitrosofenfluramine	Acute hepatitis; submassive or massive hepatic necrosis	11, 14
Green tea extracts (Exolise; Hydroxycut; The Right Approach)	*Camellia sinesis*; ? chromium	Acute hepatocellular injury; cholestatic hepatitis	10
LipoKinetix	Usnic acid; *Ephedra* alkaloids	Acute hepatitis; acute liver failure	17, 19
Ma huang	*Ephedra* alkaloids	Acute hepatitis; histology and autoantibody profile can mimic autoimmune hepatitis	17, 19, 26, 27
Pure usnic acid; Kombucha mushroom	Usnic acid	Acute liver failure	15, 22
Teucrium chamaedrys (germander)	Neoclerodane diterpenes	Acute and chronic hepatitis; zone 3 necrosis; hepatic fibrosis; cirrhosis	7
Teucrium capitatum		Acute liver failure	31
Teucrium polium (golden germander)		Zone 3 hepatic necrosis; acute liver failure; hepatic fibrosis	32

Exolose, Arkopharma, Carros, France.

Besides these reported cases, over 800 reports of hepatic injury with herbal weight loss supplements have been documented by the Japanese Health Ministry.[14] Besides Chaso (21 cases) and Onshido (135 cases), other *N*-nitrosofenfluramine-containing compounds listed include Sennomotokounou (over 100 cases) and LipoKinetix (Syntrax, Cape Girardeau, MO, USA), which is discussed later. The low frequency of liver injury among users of these products raises the likelihood of individual susceptibility to this adverse reaction. To test this hypothesis, the prevalence of CYP2C19 polymorphisms was examined in affected individuals; CYP2C19 is involved in *N*-nitrosofenfluramine metabolism. One of two Japanese patients tested carried the CYP2C19 poor metabolizer phenotype.[14] While this observation is consistent with the concept of a genetically determined reaction, it should be noted that up to 14% of the Japanese general population carry this metabolic variant. Further, acute hepatitis associated with Sennomotokounou has been documented in persons also carrying the CYP2C19 extensive metabolizer phenotype.[14] Therefore, a definitive relationship with a specific cytochrome polymorphism remains to be established.

Usnic acid

Usnic acid is derived from lichen. It has antimicrobial, anti-inflammatory and anti-proliferative properties and is marketed in a variety of different formulations such as skin creams, mouthwashes, and toothpastes.[15]

In 2002, Favreau *et al*. reported seven patients who developed acute hepatitis after using LipoKinetix.[16] This dietary supplement contains sodium usniate (usnic acid), norephedrine, yohimbine, 3, 5-diiodothyronine and caffeine; both usnic acid and ephedra alkaloids (see also Ma huang, which is discussed later) have been previously associated with severe liver injury.[17–19] Five of the patients were Japanese nationals. Symptoms of acute hepatitis, such as jaundice, abdominal pain and fatigue, were reported within 1 month in most patients (range, 10 days to 12 weeks). Peak serum transaminase levels ranged from 400 to 14 000 U/L with a mild to moderate rise in bilirubin (38–250 μmol/L). Three patients developed acute liver failure but eventually recovered. Recovery was complete within 3 months. Liver histology was not available.

Ascribing the liver toxicity to usnic acid itself is difficult because LipoKinetix contains ephedra alkaloids as well. However, the use of usnic acid alone has been implicated in other cases of severe hepatic injury.[20] A 28-year-old woman developed acute liver failure within a month of commencing usnic acid (Pure Usnic acid, Industrial strength™; AAA services, Frazer Park, CA, USA) to lose weight. She subsequently underwent orthotopic liver transplantation. The liver explant showed extensive hepatic parenchymal collapse.[20] In less severe cases, panacinar hepatitis with bridging hepatic necrosis has been observed.[21] Usnic acid is also present in Kombucha Tea (also known as Manchurian mushroom tea, Manchurian Fungus tea). This is a beverage made by brewing Kombucha mushroom in sweet black tea. The 'mushroom' is a symbiotic colony of several yeasts and bacteria held together by a thin membrane. Several cases of acute hepatitis were attributed to its use in the 1990s.[22] It is interesting to note that lactic acidosis was highlighted in early reports of toxicity with this compound.[22] This is suggestive of mitochondrial toxicity, which is consistent with the known profile of usnic acid cytotoxicity. Thus, *in vitro* studies have shown that usnic acid can uncouple mitochondrial oxidative phosphorylation and generate oxidative stress.[23] A direct hepatotoxic effect analogous to carbon tetrachloride-induced liver toxicity has also been described.[23] Finally, on the basis of a case report detailing three sisters who presented with acute hepatitis, it has been suggested that an inherent susceptibility to this adverse reaction could be important in some cases.[24]

Ephedra alkaloids (Ma huang)

In traditional herbalist practice, ephedra-containing compounds are prescribed as nasal decongestants and bronchodilators. Marketing ephedra-based products (Ma huang, metabolife, herbal ecstasy, yellow astringent) as slimming aids is a contemporary trend. In recent years, intake of ephedra alkaloids has been linked to serious cardiac toxicity, including myocardial infarction and arrhythmias and also with neuropsychiatric disorders.[25] This has led regulatory authorities, including the Food and Drug Administration, USA, to call for restrictions on their sale.

The first reports of hepatotoxicity included two cases of acute hepatitis in 1996 and 2001.[17,19] The first involved a 33-year-old

woman who developed acute hepatitis 3 weeks after using Ma huang. A liver biopsy showed diffuse hepatic necrosis. Liver tests normalized over 4 months. The second patient was a 58-year-old woman who developed acute liver failure 4.5 months after commencing Ma huang. Features suggestive of autoimmune hepatitis were present, including smooth muscle antibodies (SMA; 1:320). The liver histology description of chronic hepatitis was considered to be compatible with autoimmune hepatitis and a trial of corticosteroids was initiated. However, she failed to respond, was then listed for a liver transplant but recovered spontaneously. Subsequent publications have reiterated the potential for severe liver injury with Ma huang.[26,27] In 2004, Neff and colleagues presented 10 cases drawn from several North American liver transplant centers.[10] All of their subjects had varying degrees of hepatic encephalopathy (mostly grade 1) with marked jaundice (bilirubin > 650 μmol/L in some cases) and coagulopathy. Three patients progressed to grade 4 encephalopathy; of these two underwent liver transplantation and one died. The other seven patients recovered within 2 months. Liver explant appearances were those of panacinar necrosis. In milder cases, centrilobular necrosis was noted.

Autoantibodies (antinuclear antibodies [ANA] and/or SMA) are present in some cases leading to suggestions that this hepatic reaction is immune-mediated. Others have postulated that excessive hepatic iron may be involved.[18] This proposal was based on a report of liver injury in a Ma huang user who had coexisting hepatic iron overload (C282Y-H63D compound heterozygote).[18] However, hepatic siderosis has not been observed in other cases.

Teucrium polium

The genus *Teucrium*, comprising over 300 plant species, is endemic to the Mediterranean region and the Middle East. Its derivates are dispensed for the treatment of obesity, hypercholesterolemia, and diabetes, as well as for their anti-inflammatory, antipyretic and diuretic properties.

Teucrium-associated hepatotoxicity was first recognized with germander (*T. chamaedrys*). In 1992, Larrey and colleagues reported over 30 cases of acute liver injury associated with intake of germander capsules or herbal tea preparations.[7,9] In some individuals, chronic hepatitis or cirrhosis was evident at presentation, and chronicity was particularly likely with continued drug ingestion after the onset of symptoms. Middle-aged women comprised the majority of reported cases. They had been using the herbal remedy for 3–18 weeks. Most of those affected have eventually recovered but there have been deaths due to acute liver failure, and cirrhosis has been observed.

Germander toxicity is attributed to reactive metabolites (epoxides) generated by CYP3A metabolism of its constituent neoclordane diterpenoids (chiefly Teucrin A).[28] In rat hepatocytes, these epoxides can deplete hepatic glutathione and cytoskeleton-associated protein thiols. These processes culminate in the formation of plasma membrane blebs and apoptosis. However, other lines of evidence implicate immune-mediated pathways in initiating liver injury. When rechallenged with germander, a rapid rise of serum transaminases was observed in approximately half of these cases. In other cases, autoantibodies (antinuclear, smooth muscle and anti-mitochondrial M2) were present.[29] In particular, a specific autoantibody (antimicrosomal epoxide hydrolase) was identified from sera of long-term drinkers of germander tea. The target for this autoantibody is an epoxide hydrolase on the hepatocyte surface.[30]

A few years (1995) after the germander mini-epidemic, extracts from a related species (*T. capitatum*) were also linked with instances of acute liver failure in France.[31] Within the last 5 years, a report from Greece detailing 11 persons presenting with acute hepatitis has highlighted the hepatic effects of yet another related herb, *T. polium.* [32] In these cases, the latent period to the onset of symptoms was less than 6 months. Serum transaminases were moderately to markedly elevated (30–150 times the upper limit of normal [ULN]). Liver biopsies showed zone 3 necrosis, acute hepatitis with bridging necrosis or occasionally massive hepatocyte necrosis. While most affected individuals recovered spontaneously, the consequence of this adverse herbal drug effect can be severe; one patient underwent emergency liver transplantation for acute liver failure. Importantly, several furano neoclerodane diterpenoids structurally similar to Teucrin A (cf. germander) have been isolated from *T. polium.*

Other hepatotoxic terpenoid-containing compounds

Terpenes are isoprene unit-containing cyclical hydrocarbons that are widely distributed throughout the vegetable kingdom. As mentioned earlier, their metabolism by cytochrome P450-mediated oxidation can result in unstable epoxides. In addition to *Teucrium* species, another neoclerodane diterpenoid-containing hepatotoxic herbal product is skullcap (*Scutellaria lateriflora*). Herbs containing triterpenoids have also been associated with liver toxicity. Examples include Syo-saiko-to and *Centella asiatica.*

Syo-saiko-to contains glycyrrhizin, a triterpenic saponoside. This herbal constituent is often prescribed for individuals with chronic viral hepatitis but, paradoxically, has itself been associated with inducing confluent or focal hepatic necrosis, microvesicular steatosis and hepatic granulomas.[7] This herbal mixture remains one of the mostly widely prescribed herbs for the treatment of liver disorders in China, Taiwan and Japan, and should therefore always be considered in cases of unexplained acute hepatitis. Known also as xiao-chai-hu-tang,[33] this remedy is a mixture of seven herbs including *Glycyrrhiza* root and *Scutellaria baicalensis* (Chinese skullcap). The latter differs from *Scutellaria laterifora* (American skullcap), which has been associated with hepatic veno-occlusive disease.

Centella asiatica is used in traditional Indian medicine (ayurvedic medicine) to treat a variety of disorders, including obesity, leprosy and skin wounds. Three cases of acute hepatitis were recorded with use of *C. asiatica* in Argentina.[34] All three affected persons were female, 49–61 years. They had used this slimming remedy for 3–8 weeks. The clinical and biochemical profile was in keeping with an acute hepatocellular process, but granulomatous hepatitis was reported in liver biopsies from two of these cases. In the third patient, chronic hepatitis with cirrhotic transformation was observed in the liver biopsy. This patient recalled developing abnormal liver tests with the same product 1 year earlier. *C. asiatica* should therefore be added to the list of herbal agents that are known to cause both acute as well as chronic liver injury ('hepatitis'). All three cases recovered after discontinuing the agent together with treatment with ursodeoxycholic acid and/or prednisone, but it is not apparent that these are essential.

It seems possible that germander-type reactive metabolite-induced liver injury could invoke this idiosyncratic reaction. The active principles of *C. asiatica* are pentacyclic triterpenic saponosides, chiefly asiaticoside and madecassoside.[35] Here too, immune mechanisms have been implicated in the pathogenesis. In particular, inadvertent reuse has been followed by recurrent hepatitis and development of autoantibodies (SMA in titers of 1:160 and AMA in titers of 1:320).

Green tea extracts

Chinese green tea extracts (*Camellia sinensis*) are widely consumed for their purported health benefits. Reports of hepatotoxicity have cast doubts on their general safety.[36] A 37-year-old Hispanic woman presented with a 10-day history of diffuse abdominal pain and jaundice. Four months earlier, she had started using a dietary supplement (Right Approach Complex®; Pharmanex, Provo, UT, USA). Peak serum transaminases levels were elevated over 40 × ULN (1788 IU/mL); the ANA result was 1:40. No other causes for liver disease were identified. Liver histology showed marked interface necrosis and mild lobular hepatitis. The liver tests improved spontaneously over 6 weeks. One year later, she presented again with acute hepatitis. On questioning, she admitted to reusing the same product for a month before presentation. Biochemical resolution was complete within 6 months. The documented positive rechallenge along with a compatible temporal profile and exclusion of other liver disorders strongly implicates the herbal remedy as the causative agent in this case. Similar cases have been reported from France, Spain and Italy with other compounds containing green tea extracts.[37–39] Two cases of acute liver failure have been also been reported;[40,41] liver explants showed massive or submassive necrosis.

High concentrations of green tea extracts have been shown to be toxic to rat hepatocytes *in vitro*.[42] Mitochondrial toxicity and formation of reactive oxygen species (ROS) have also been demonstrated with epigallocatechin-3-gallate, a key constituent of green tea extracts.[43] However, the relatively low bioavailability of some of the key constituents after oral exposure suggests that other pathways may be involved.

Hydroxycut (MuscleTech, Mississauga, Ontario, Canada), another herbal slimming aid derived from green tea extracts has been associated with two instances of hepatotoxicity.[44] In the first case, acute hepatocellular injury was noted, and the second showed cholestasis and portal inflammation. Attributing toxicity to a single constituent of a multiple constituent herbal product is difficult. While it is speculated that green tea extracts are the main toxic ingredient (based on reports of similar cases), others have pointed out that chromium (also present) could be responsible.[45] The herbal products that had been used by these two patients were not analyzed. Nonetheless, it is important to report these cases to flag these sentinel events for future reference.

Update on known and emerging herbal hepatotoxins

Table 2 summarizes the hepatotoxicity of established and emerging hepatotoxins. Some of these are discussed below.

Black cohosh (*Cimicifuga racemosae*, Actaea racemosa)

Widely used in managing menopause-associated vasomotor symptoms, Black cohosh is perceived as being a phytoestrogen. However, detailed analysis of product samples across the USA has not identified the presence of estrogenic compounds.

There are only a few published reports of acute hepatitis with Black cohosh.[46–50] However, the degree of liver injury in affected individuals can be quite severe; of the six reported cases, four had to undergo liver transplantation. Liver explants showed massive or submassive hepatic necrosis and bridging fibrosis. In one case, a trial of corticosteroids was successfully initiated on the basis of positive ANA (1:640) and a liver biopsy compatible with autoimmune hepatitis.[49]

Besides these published cases, drug regulatory agencies in Australia, USA, UK and Germany have received reports of more than 40 instances of hepatotoxicity associated with Black cohosh.[51] Causality was established in some but not all reported cases, but the evidence has been considered to be persuasive enough to mandate changes in product labeling.

The mechanism of liver injury is unclear but black cohosh also contains triterpene glycosides, which were discussed earlier. The presence of tissue eosinophilia in some cases suggest that immunoallergic mechanisms may also contribute to liver injury.

Boh-Gol-Zhee

This herbal remedy consists of dried matured seeds from *Psoralea corylifolia*, a leguminous plant. In 2005, a 44-year-old South Korean woman presented with acute cholestatic hepatitis after ingesting this preparation with black tea every hour for 7 weeks.[52] Liver biopsy showed zone 3 centrilobular hepatic necrosis with hemorrhage, cholestasis and an inflammatory infiltrate. The toxic ingredient is unknown. The constituents of Boh-Gol-Zee include, among others, fatty oil, resin, bakuchiol and psoralen. Interestingly, genistein, a widely used phytoestrogen, is also derived from the leaves of *Psoralea corylifolia* and conceivably could induce estrogen-type cholestasis. However, genistein is not a recognized constituent of this herbal compound. The patient under discussion had been using doses over 10 times that recommended by the manufacturer.

Kava

For over 2000 years in the South Pacific, the rhizome and roots of *Piper methysticum*, a shrub of the pepper plant family have been used to prepare a recreational and ceremonial beverage (Kava, Kava Kava). It is also widely available as an over-the-counter anxiolytic or sedative. Reversible increases in gamma glutamyl transpeptidase (GGT) and alkaline phosphatase have been reported among indigenous communities consuming Kava.[53] These are considered to represent hepatic adaption rather than toxicity.

Kava-associated acute liver failure was first reported in 1998. Since then, over 60 cases of hepatotoxicity have been attributed to Kava.[54,55] Confounding factors (including alcohol) were present in some but not all cases. Overall, hepatic injury appears to be an infrequent side-effect of Kava; the frequency of liver injury has

Table 2 Updated account of established and emerging herbal hepatotoxins

Herbal remedy	Indications	Possible toxic constituent(s)	Pattern of liver injury
Atractylis gummifera	Purgative; emetic; diuretic	Potassium atractylate; and gummiferin	Acute liver failure
Boh-Gol-Zhee	Bone disorders	*Psoralea corylifolia*	Zone 3 hepatic necrosis; cholestatic hepatitis
Chaparral leaf	Multiple uses	*Larrea tridentata*	Zone 3 hepatic necrosis; massive hepatic necrosis; chronic hepatitis; cholestasis
Chinese herbal medicines (see text)	Multiple; skin diseases; viral hepatitis	Many; *Dictamnus dasycarpus* present in six cases	Liver injury (no histology); acute hepatitis; hepatic VOD; vanishing bile duct syndrome
Comfrey; gordolobo yerba tea; maté tea; Chinese herbal tea	Health tonic	Pyrrolizidine alkaloids	Hepatic VOD
Camphor	Rubefacient	Cyclic terpenes	Abnormal liver tests; encephalopathy
Carp capsules (raw carp gallbladder)	Rheumatism; visual acuity	Cyprinol	Liver enzyme changes (no biopsy) with acute renal failure; hepatic necrosis (in rats)
Fu Fang Qing Dai Wan	Psoriasis	Unknown (multiple herbs)	Acute hepatitis
Greater Celandine	Gallstones	*Chelidonium majus*	Acute hepatitis; cholestatic hepatitis; fibrosis
'Green juice'	Dietary supplement	Unknown; has vegetable extracts; micronutrients	Granulomatous hepatitis
Jin Bu Huan Anodyne tablets	Sedation; analgesic	*Lycopodium serratum*	Acute and chronic hepatitis; steatosis; fibrosis
Kava	Anxiety disorders	Kavalactones or kava alkaloids	Diffuse hepatocellular necrosis; cholestatic hepatitis; isolated γ-GTP increase
Linghzi	Multiple	*Ganoderma lucidum*	Acute cholestatic hepatitis
Margosa oil	Health tonic	*Azadirachta indica*	Reye's syndrome
Mixed preparations: mistletoe; skullcap; valerian	Herbal tonics	Unknown;? *Scutellaria*. Skullcap has diterpenoids	Liver injury (no histological studies)
'Natural laxatives'	Cathartic	Senna; podophyllin; aloin	Senna (acute hepatitis; acute cholestatic hepatitis)
		Cascara sagrada (anthraquinones)	Acute cholestatic hepatitis; bridging hepatic fibrosis
		Isabgol	Giant cell hepatitis
Noni juice	Health tonic	*Morinda citrifolia* ? anthraquinone	Acute hepatitis; zone 3 cholestasis; subacute liver failure (confounding factors present)
Oil of cloves	Dental pain	Eugenol	Dose-dependent hepatotoxin; zonal necrosis
Pennyroyal oil (squawmint)	Abortifacient	Pulegone metabolites	Confluent hepatocellular necrosis
Prostata	Prostatism	Saw palmetto	Hepatitis; fibrosis
Shark cartilage	Food supplement	Not identified	Abnormal liver tests (no histology)
Sho-saiko-to (TJ-9) [xiao-chai-hu-tang]	Health tonic; viral hepatitis	*Scutellaria* spp.; glycyrrhizin; others	Zonal/bridging necrosis; hepatic fibrosis; microvesicular steatosis; hepatic granuloma
Zulu remedy (Impila)	Health tonic	*Callilepsis laureola*	Hepatic necrosis

Further accounts of many of these agents are given in references.[3,4,6,7,73,74]

γ-GTP, γ-glutamyl transpeptidase; VBDS, vanishing bile duct syndrome; VOD, veno-occlusive disease.

been estimated at 0.24–0.26 per million daily doses.[54] Most reported cases have occurred in users of alcohol or acetone-extracts of the herb and only very rarely (two cases) with traditional aqua-based preparations of kava.[56]

Although infrequent, Kava can be associated with severe liver injury. Worldwide, at least 11 patients have developed acute liver failure.[55] More women than men have been affected (female : male ratio, 3:1). A wide variation in the time to onset of symptoms has been observed (range, 2 weeks to 2 years; median 4.5 months). Liver explants have shown panacinar necrosis. In less severe cases, cholestatic or lobular hepatitis was noted. Positive rechallenge has been documented.

The active ingredients in kava are collectively termed kava pyrones (or kavalactones). The mechanism of liver injury is unclear, but a number of different potential mechanisms have been suggested.[57] These include kavalactone-induced inhibition of CYP enzymes (such as CYP1A2, CYP2D6), inhibition of cyclooxygenases COX-1 and COX-2, or depletion of hepatic glutathione. It

has been speculated that Europid populations are at greater risk of liver toxicity than Pacific islanders because CYP2D6 deficiency is more common among the former (8% *vs* approximately 1%, respectively). The absence of dose dependency hints at the possibility of an immuno-allergic mode of liver injury in some cases. This view is supported by the presence of autoantibodies, eosinophilia, positive lymphocyte transformation test, and therapeutic success with corticosteroids in some reports.

Recent studies have questioned the relevance of kavalactone content to the hepatic effects of Kava.[58] Studies of kavalactone content between aqueous and non-aqueous extracts of kava have yielded conflicting results, with some showing lower content among the former, whereas others have not observed significant differences. It has been suggested that pipermethystine is probably central to its liver toxicity. This kava alkaloid is mainly present in the aerial portions of the plant, parts of which are not usually included in root-based traditional Kava preparations. In human hepatocellular carcinoma cell lines (HepG2), pipermethystine was found to be significantly more toxic than kavalactones. Induction of cell death by disrupting mitochondrial function has been demonstrated.[58]

Pyrrolizidine alkaloids

Cases of pyrrolizidine alkaloids (PA)-induced hepatic veno-occlusive disease (HVOD) are now less frequently reported. In contemporary clinical practice, most instances of HVOD in clinical practice are now associated with thrombophilic or myeloproliferative disorders, and in the context of hematopoietic stem cell transplantation.[59] Even so, vigilance is necessary, particularly in endemic areas. For instance, as recently as 2000, Steenkamp and colleagues reported on 20 children with PA toxicity presenting to two South African hospitals.[60] As expected, 94% of those presenting with acute HVOD, had massive ascites and hepatomegaly. Mortality was high (45%). Many of the survivors had hepatosplenomegaly suggestive of residual portal hypertension. A new urine colorimetric method has been developed so that they can rapidly identify cases of acute PA toxicity presenting within 72 h.[60]

Over 300 varieties of PA have been identified from over 6000 plants belonging to the *Compositae*, *Boraginaceae* and *Leguminosae* families. Therefore, reports of liver toxicity from hitherto unknown preparations containing PA are to be expected. Four cases of HVOD were traced to the ingestion of Gynura root (*Gymura segetum*).[61,62] This herb derived from the *Compositae* family is used in traditional Chinese medicine for pain relief and vascular insufficiency. Over 20 cases of HVOD are described in Chinese language journals. HVOD, the signature lesion of PA liver injury should alert the clinician about possible PA toxicity. This often requires a diligent search, as illustrated by a recent case of a preterm neonate with HVOD. The causative PA were eventually traced to an herbal cooking additive.[63] This report also extends the spectrum of PA hepatotoxicity to include intrauterine HVOD.

Shou-Wu-Pian

Derived from the powdered root of *Polygonum multiflorum* (fleeceflower root), Shou-Wu-Pian is claimed to have 'anti-aging' properties and is used to treat premature graying of the hair. The name Shou-Wu-Pian is roughly translated as 'Mr Black hair'.

A few cases of acute hepatitis[64–67] have accrued with this preparation. Liver histology data are scanty but features of acute cholestatic hepatitis were described in one case. Affected individuals have recovered after discontinuing the product. Positive rechallenge has also been documented.

The toxicity of this herbal compound has been attributed to its anthraquinone content. Other anthraquinone-containing compounds that have been associated with acute hepatocellular injury include popular herbal laxatives such as senna (acute hepatitis, acute cholestatic hepatitis) and cascara (acute cholestatic hepatitis, bridging hepatic fibrosis)[68,69] as well as synthetic drugs such as mitoxantrone and Danthron.[67] Others have demonstrated only trace amounts of anthraquinone in Shou-Wu-Pian and attribute the toxicity to its stilbene glycoside content.[67]

Severe acute hepatocellular injury has also been described with Shen Min, a 'hair nutritional supplement' containing a mixture of vitamins and herbs including *Polygonum multiflorum.*[70] The authors of the report have considered *P. multiflorum* to be the likely cause of acute hepatitis. However, this product also contains Black cohosh (which has been described earlier).

Herbalife®

Marketed for weight reduction and for 'enhancing well-being' in over 60 countries, these herbal products were implicated in two case reports of acute liver injury in a total of 22 patients from Switzerland and Israel.[71,72] Most of those affected were female (median age, 50 years). The latent period to onset of symptoms varied from 5 to 11 months (range 0.5–144 months). Liver histology included acute hepatitis, portal inflammation with eosinophils, bile ductular reaction, cholestasis and confluent hepatic necrosis. Unusual lesions included giant cell hepatitis (in the liver explant) and sinusoidal obstruction syndrome. The toxic components have not been identified. Despite the global use of these products, the restricted geographical locations of reported cases could reflect contamination or differences in manufacturing processes. For example, lesions such as sinusoidal obstruction raise the suspicion of pyrrolizidine alkaloid contamination. Most patients have recovered after discontinuation. However, cirrhosis and rarely acute liver failure have also been observed. Persons with underlying liver disease may be susceptible as shown by exacerbation of liver disease in two patients with primary biliary cirrhosis and chronic hepatitis B, respectively. Positive rechallenge has been described in five cases.

Discussion

Underreporting to regulatory authorities is a repeated theme in epidemiological studies of drug-induced liver injury. Similar considerations likely apply to herbal remedy-related toxicity. In many countries, the latter continue to be labeled as dietary supplements and therefore subject to less scrutiny than prescribed drugs. However, growing public concern has led to instigation of programs where adverse drug reactions can be catalogued (e.g. MEDWATCH). A welcome development has been the issue of physician alerts not only for drugs but also for toxic herbs. Further, statutory warning labels are now required for some products, and standards of good manufacturing practice.

It is well documented that patients attending liver clinics are often likely to be using concurrent herbal products. In many cases, this is not disclosed to the treating doctor, or physicians may not routinely enquire about TCM and other CAM. Unexplained worsening of stable chronic liver disease should always prompt direct questioning for the use of herbal remedies. In extreme cases, this may involve observation after admission to hospital, questioning family members and searching bedside lockers. Occasionally, the causative agent may be an unlisted constituent of the herbal compound. This is illustrated by a recent case series from Singapore documenting acute flares of previously stable chronic hepatitis B in persons using herbal products containing corticosteroids.[8]

Finally, physician and patient awareness remain central to the early identification of herbal toxicity. As for conventional medicines, dose recommendations should not be exceeded, and patients should be advised to use only reputable brands subject to standards of good medical practice, preferably under supervision of a traditional medicine practitioner (if patients insist on using these compounds). They should also be advised of possible adverse effects and to report these early, even if non-specific in nature. Reporting of unusual reactions to drug regulatory authories is imperative. Ideally, attempts should be made to procure the implicated products and have them analyzed for their chemical composition. More research is also required to identify the culprit toxic molecules in herbal medicines and to understand hepatotoxic mechanisms. Only then can logical therapies be developed.

References

1 De Smet PA. Herbal remedies. *N. Engl. J. Med.* 2002; **19**: 2046–56.
2 Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. *Med. J. Aust.* 2004; **181**: 222–5.
3 Larrey D, Pageaux GP. Hepatotoxicity of herbal remedies and mushrooms. *Semin. Liver Dis.* 1995; **15**: 183–8.
4 Stedman C. Herbal hepatotoxicity. *Semin. Liver Dis.* 2002; **22**: 195–206.
5 Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. *Aliment. Pharmacol. Ther.* 2006; **24**: 1179–86.
6 Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. *J. Hepatol.* 2005; **43**: 901–10.
7 Chitturi S, Farrell GC. Herbal hepatotoxicity: an expanding but poorly defined problem. *J. Gastroenterol. Hepatol.* 2000; **15**: 1093–9.
8 Wai CT, Tan BH, Chan CL *et al.* Drug-induced liver injury at an Asian center: a prospective study. *Liver Int.* 2007; **27**: 465–74.
9 Larrey D, Vial T, Pauwels A *et al.* Hepatitis after germander (*Teucrium chamaedrys*): Another instance of herbal medicine hepatotoxicity. *Ann. Intern. Med.* 1992; **117**: 129–32.
10 Neff GW, Reddy KR, Durazo FA, Meyer D, Marrero R, Kaplowitz N. Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. *J. Hepatol.* 2004; **41**: 1062–4.
11 Adachi M, Saito H, Kobayashi H *et al.* Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido. *Ann. Intern. Med.* 2003; **139**: 488–92.
12 Nakagawa Y, Tayama S, Ogata A, Suzuki T, Ishii H. ATP-generating glycolytic substrates prevent N-nitrosofenfluramine-induced cytotoxicity in isolated rat hepatocytes. *Chem. Biol. Interact.* 2006; **164**: 93–101.
13 Nakagawa Y, Suzuki T, Kamimura H, Nagai F. Role of mitochondrial membrane permeability transition in N-nitrosofenfluramine-induced cell injury in rat hepatocytes. *Eur. J. Pharmacol.* 2006; **529**: 33–9.
14 Kawaguchi T, Harada M, Arimatsu H *et al.* Severe hepatotoxicity associated with a N-nitrosofenfluramine-containing weight-loss (Suppl.): report of three cases. *J. Gastroenterol. Hepatol.* 2004; **19**: 349–50.
15 Ingolfsdottir K. Usnic acid. *Phytochemistry* 2002; **61**: 729–36.
16 Favreau JT, Ryu ML, Braunstein G *et al.* Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann. Intern. Med.* 2002; **136**: 590–5.
17 Nadir A, Agrawal S, King P, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, Ma huang. *Am. J. Gastoenterol.* 1996; **91**: 1436–8.
18 Borum ML. Fulminant exacerbation of autoimmune hepatitis after the use of Ma huang [Letter]. *Am. J. Gastroenterol.* 2001; **96**: 1654–5.
19 Bajaj J, Knox JF, Komorowski R, Saeian K. The irony of herbal hepatitis. Ma-huang induced hepatotoxicity associated with compound heterozygosity for hereditary hemochromatosis. *Dig. Dis. Sci.* 2003; **48**: 1925–8.
20 Durazo FA, Lassman C, Han SH *et al.* Fulminant liver failure due to usnic acid for weight loss. *Am. J. Gastroenterol.* 2004; **99**: 950–2.
21 Sanchez W, Maple JT, Burgart LJ, Kamath PS. Severe hepatotoxicity associated with use of a dietary supplement containing usnic acid. *Mayo Clin. Proc.* 2006; **81**: 541–4.
22 Centers for Disease Control. Unexplained severe illness possibly associated with consumption of Kombucha tea – Iowa, 1995. *MMWR* 1995; **44**: 892–900.
23 Han D, Matsumaru K, Rettori D, Kaplowitz N. Usnic acid-induced necrosis of cultured mouse hepatocytes: inhibition of mitochondrial function and oxidative stress. *Biochem. Pharmacol.* 2004; **67**: 439–51.
24 Hsu LM, Huang YS, Chang FY, Lee SD. 'Fat burner' herb, usnic acid, induced acute hepatitis in a family. *J. Gastroenterol. Hepatol.* 2005; **20**: 1138–9.
25 Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N. Engl. J. Med.* 2000; **343**: 1833–8.
26 Skoulidis F, Alexander GJ, Davies SE. Ma huang associated acute liver failure requiring liver transplantation. *Eur. J. Gastroenterol. Hepatol.* 2005; **17**: 581–4.
27 Estes JD, Stolpman D, Olyaei A *et al.* High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch. Surg.* 2003; **138**: 852–8.
28 Fau D, Lekehal M, Farrell G *et al.* Diterpenoids from germander, an herbal medicine, induce apoptosis in isolated rat hepatocytes. *Gastroenterology* 1997; **113**: 1334–46.
29 Polymeros D, Kamberoglou D, Tzias V. Acute cholestatic hepatitis caused by Teucrium polium (golden germander) with transient appearance of antimitochondrial antibody. *J. Clin. Gastroenterol.* 2002; **34**: 100–1.
30 De Berardinis V, Moulis C, Maurice M *et al.* Human microsomal epoxide hydrolase is the target of germander-induced autoantibodies on the surface of human hepatocytes. *Mol. Pharmacol.* 2000; **58**: 542–51.
31 Mattei Dourakis SP, Papanikolaou IS *et al.* Acute hepatitis associated with herb (Teucrium capitatum L.) administration. *Eur. J. Gastroenterol. Hepatol.* 2002; **14**: 693–5.
32 Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by Teucrium polium L: report

of two cases and review of the literature. *Eur. J. Gastroenterol. Hepatol.* 2007; **19**: 507–11.
33 Hsu LM, Huang YS, Tsay SH, Chang FY, Lee SD. Acute hepatitis induced by Chinese hepatoprotective herb, xiao-chai-hu-tang. *J. Chin. Med. Assoc.* 2006; **69**: 86–8.
34 Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. *Rev. Esp. Enferm. Dig.* 2005; **97**: 115–24.
35 Brinkhaus B, Lindner M, Schuppan D *et al.* Chemical, pharmacological and clinical profile of the East Asian medical plant centella asiatica. *Phytomedicine* 2000; **7**: 427–48.
36 Bonkovsky HL. Hepatotoxicity associated with supplements containing hinese green tea (Camellia sinensis). *Ann. Intern. Med.* 2006; **144**: 68–71.
37 Pedros C, Cereza G, Garcia N, Laporte JR. Liver toxicity of *Camellia sinensis* dried etanolic extract [Letter]. *Med. Clin. (Barc)* 2003; **121**: 598–9.
38 Thiolet C, Mennecier D, Bredin C *et al.* Acute cytolysis induced by Chinese tea [Letter]. *Gastroenterol. Clin. Biol.* 2002; **26**: 939–40.
39 Vial T, Bernard G, Lewden B, Dumortier J, Descotes J. Acute hepatitis due to Exolise, a *Camellia sinensis*-derived drug [Letter]. *Gastroenterol. Clin. Biol.* 2003; **27**: 1166–7.
40 Molinari M, Watt KD, Kruszyna T *et al.* Acute liver failure induced by green tea extracts: case report and review of the literature. *Liver Transpl.* 2006; **12**: 1892–5.
41 Gloro R, Hourmand-Ollivier I, Mosquet B *et al.* Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. *Eur. J. Gastroenterol. Hepatol.* 2005; **17**: 1135–7.
42 Schmidt M, Schmitz HJ, Baumgart A *et al.* Toxicity of green tea extracts and their constituents in rat hepatocytes in primary culture. *Food Chem. Toxicol.* 2005; **43**: 307–14.
43 Galati G, Lin A, Sultan AM, O'Brien PJ. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. *Free Radic. Biol. Med.* 2006; **40**: 570–80.
44 Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut. *Ann. Intern. Med.* 2005; **142**: 477–8.
45 Gregory PJ. Chromium polynicotinate linked to hepatotoxicity (electronic letter). *Ann. Int. Med.* 2005; **142**. Cited 1 Jul 2007. Available from URL: http://www.annals.org/cgi/eletters/142/6/477#1445
46 Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med. J. Aust.* 2002; **177**: 440–3.
47 Lontos S, Jones RM, Angus PW, Gow PJ. Acute liver failure associated with the use of herbal preparations containing black cohosh. *Med. J. Aust.* 2003; **179**: 390–1.
48 Levitsky J, Alli TA, Wisecarver J, Sorrell MF. Fulminant liver failure associated with the use of black cohosh. *Dig. Dis. Sci.* 2005; **50**: 538–9.
49 Cohen SM, O'Connor AM, Hart J, Merel NH, Te HS. Autoimmune hepatitis associated with the use of black cohosh: a case study. *Menopause* 2004; **11**: 575–7.
50 Lynch CR, Folkers ME, Hutson WR. Fulminant hepatic failure associated with the use of black cohosh: a case report. *Liver Transpl.* 2006; **12**: 989–92.
51 New labelling requirements and consumer information for medicines containing Black cohosh. Cited 1 Jul 2007. Available from URL: http://www.tga.gov.au/cm/0705blkcohosh.htm.
52 Nam SW, Baek JT, Lee DS, Kang SB, Ahn BM, Chung KW. A case of acute cholestatic hepatitis associated with the seeds of Psoralea corylifolia (Boh-Gol-Zhee). *Clin. Toxicol. (Phila)* 2005; **43**: 589–91.
53 Clough AR, Bailie RS, Currie B. Liver function test abnormalities in users of aqueous kava extracts. *J. Toxicol. Clin. Toxicol.* 2003; **41**: 821–9.
54 Stickel F, Baumuller HM, Seitz K *et al.* Hepatitis induced by Kava (Piper methysticum rhizoma). *J. Hepatol.* 2003; **39**: 62–7.
55 Hepatic toxicity possibly associated with kava-containing products – United States, Germany, and Switzerland, 1999–2002. *MMWR Morb. Mortal. Wkly Rep.* 2002; **51**: 1065–7.
56 Russmann S, Barguil Y, Cabalion P *et al.* Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia. *Eur. J. Gastroenterol. Hepatol.* 2003; **15**: 1033–6.
57 Clouatre DL. Kava kava: examining new reports of toxicity. *Toxicol. Lett.* 2004; **150**: 85–96.
58 Nerurkar PV, Dragull K, Tang CS. In vitro toxicity of kava alkaloid, pipermethystine, in HepG2 cells compared to kavalactones. *Toxicol. Sci.* 2004; **79**: 106–11.
59 Chojkier M. Hepatic sinusoidal–obstruction syndrome: toxicity of pyrrolizidine alkaloids. *J. Hepatol.* 2003; **39**: 437–46.
60 Steenkamp V, Stewart MJ, Zuckerman M. Clinical and analytical aspects of pyrrolizidine poisoning caused by South African traditional medicines. *Ther. Drug Monit.* 2000; **22**: 302–6.
61 Dai N, Yu YC, Ren TH, Wu JG, Jiang Y, Shen LG, Zhang J. Gynura root induces hepatic veno-occlusive disease: a case report and review of the literature. *World J. Gastroenterol.* 2007; **13**: 1628–31.
62 Dai HF, Gao Y, Yang M, Yu CH, Gu ZY, Chen WX. Hepatic veno-occlusive disease induced by Gymura segetum: report of two cases. *Hepatobiliary Pancreat. Dis. Int.* 2006; **5**: 406–8.
63 Rasenack R, Muller C, Kleinschmidt M, Rasenack J, Wiedenfeld H. Veno-occlusive disease in a fetus caused by pyrrolizidine alkaloids of food origin. *Fetal Diagn. Ther.* 2003; **18**: 223–5.
64 But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from Polygonum multiflorum. *Vet. Hum. Toxicol.* 1996; **38**: 280–2.
65 Park GJ, Mann SP, Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from Polygonum multiflorum. *J. Gastroenterol. Hepatol.* 2001; **16**: 115–17.
66 Mazzanti G, Battinelli L, Daniele C *et al.* New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from Polygonum multiflorum. *Ann. Intern. Med.* 2004; **140**: W30.
67 Panis B, Wong DR, Hooymans PM, De Smet PA, Rosias PP. Recurrent toxic hepatitis in a Caucasian girl related to the use of Shou-Wu-Pian, a Chinese herbal preparation. *J. Pediatr. Gastroenterol. Nutr.* 2005; **41**: 256–8.
68 Nadir A, Reddy D, Van Thiel DH. Cascara sagrada-induced intrahepatic cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity. *Am. J. Gastroenterol.* 2000; **95**: 3634–7.
69 Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. *Lancet* 1991; **337**: 372–3.
70 Cardenas A, Restrepo JC, Sierra F, Correa G. Acute hepatitis due to shen-min: a herbal product derived from Polygonum multiflorum. *J. Clin. Gastroenterol.* 2006; **40**: 629–32.
71 Elinav E, Pinsker G, Safadi R *et al.* Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J. Hepatol.* 2007; **47**: 514–20.
72 Schoepfer AM, Engel A, Fattinger K *et al.* Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J. Hepatol.* 2007; **47**: 521–6.
73 Stadlbauer V, Fickert P, Lackner C *et al.* Hepatotoxicity of NONI juice: report of two cases. *World J. Gastroenterol.* 2005; **14**: 4758–60.
74 Millonig G, Stadlmann S, Vogel W. Herbal hepatotoxicity: acute hepatitis caused by a Noni preparation (Morinda citrifolia). *Eur. J. Gastroenterol. Hepatol.* 2005; **17**: 445–7.