NOTABLE CASES

Black cohosh and other herbal remedies associated with acute hepatitis

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Six patients presented with clinical, biochemical and histological evidence of severe hepatitis after taking herbal remedies. One patient required urgent liver transplantation for fulminant hepatic failure after the brief use of black cohosh. Five patients took a combination of herbs and presented with jaundice, fatigue and pruritus. Healthcare providers and members of the public should be aware of the potential adverse effects of these remedies. ***(MJA 2002; 177: 432-435)***

THERE HAS BEEN A STEADY RISE in the use of complementary medicine throughout the world. In 1997 it was estimated that 57% of Australians used complementary medicines, with an annual expenditure of $621 million.[1,2] Self-medication is common, with 62%–72% of patients not disclosing the use of herbal preparations to their family doctors.[3] This reluctance may be due to a perceived conflict between practitioners of conventional and alternative medicine.

Although there have been trials on the efficacy of several herbal remedies, most information is based on anecdotal evidence and reputation. Information documenting adverse reactions is based on case reports and literature reviews, as there have been few prospective trials to date.[4-7] As a result, the data available may not highlight potential adverse effects. In 1999 the Office of Complementary Medicine was created as part of the Therapeutic Goods Administration (TGA) in an attempt to regulate alternative medicine in Australia. The constituents of a herbal remedy must undergo pre-market evaluation for safety and quality before being listed on the Australian Register of Therapeutic Goods. Manufacturers of herbal products must now be licensed and need to adhere to the Therapeutic Goods Advertising Code. If a complementary medicine claims to "cure/manage or prevent" a disorder it requires high-level evidence to be registered, but if it claims to be for "symptom relief/health maintenance or health enhancement" then the product does not need formal evaluation.

With the expanding use of these remedies, the risk of serious drug interactions increases. There is some information available on common interactions,[7,8] but continued vigilance is required with the introduction of new medications.

We describe six patients with hepatotoxicity from a variety of herbal remedies. The patients were reviewed by a gastroenterologist in Queensland (P K) between 1996 and 2001. Data were collected when the patient presented and subsequent telephone inquiry clarified any other details. The individual herbal products were not analysed for their constituents.

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Clinical records

Clinical records for the six patients are summarised in Box 1. One woman used black cohosh (*Cimicifuga racemosa*) alone for one week, and the other five patients were taking various combinations of herbs for 6–18 weeks before the onset of symptoms. Four patients disclosed the use of the herbal product to their general practitioner before referral. Patient 1 was taking the herbal remedy for relief of symptoms of menopause, Patient 5 as a "liver tonic", and Patient 6 to lose weight. The others took the remedies for general health promotion. The doses varied and were not reported to exceed the dosage recommended on the package.

None of the patients had a history of excessive alcohol intake, injecting drug use, prior blood transfusion, family history of liver disease, or past history of liver or biliary tract disease. Patient 3 was taking temazepam, and Patient 4 had been taking long term low dose aspirin. No other concurrent medication was reported. Two patients had notable comorbidities: Patient 3 suffered from Huntington's chorea, and Patient 2 was diagnosed with ovarian adenocarcinoma shortly after presenting with hepatitis, but had no evidence of metastatic involvement of the liver on biopsy, computed tomography scan or at laparotomy.

All patients developed jaundice, and the pattern of liver enzyme abnormality was predominantly hepatocellular (serum alanine aminotransferase level > 1000 U/L in each), with moderate elevations in the cholestatic enzymes. Pruritus was present in three patients. The international normalised ratio [INR] was elevated in two subjects (Patient 1: INR, 4.6; Patient 2: INR, 2.4). Peripheral blood eosinophilia was not present in any of the patients.

No causes for liver disease other than the herbal remedies were found. Serology for hepatitis A (IgM, anti-HAV), hepatitis B (HBsAg) and hepatitis C (anti-HCV) was negative in each of the patients. The antinuclear antibody was positive in a titre of 1:40 in Patients 2 and 3. The smooth-muscle antibody and antimitochondrial antibody titres were negative for all patients tested (1–3, 5, 6). The iron and

1: Summary of clinical and laboratory data for six patients who developed hepatitis after taking herbal remedies

Patient (sex, age)	Herbal remedy	Time on herbs (weeks)	Time to symptoms (weeks)	Symptoms		Peak value					Time from diagnosis to normal laboratory results (weeks)	Treatment
				Symptom	Duration (weeks)	Bilirubin† (μmol/L)	ALP‡ (U/L)	AST§ (U/L)	ALT¶ (U/L)	GGT** (U/L)		
1 (F, 47)	Black cohosh	1	1	Jaundice	2	335	158	3182	2295	163	Not applicable	Liver transplant
2 (F, 43)	Skullcap;* valerian;* black cohosh; passionflower; *Angelicia sinensis*; hops; *Avema sativa*; chasteberry	N/A	N/A	Jaundice; nausea; vomiting; diarrhoea	18	284	80	1140	1500	N/A	N/A	Nil
3 (F, 75)	Skullcap; valerian;* hops	6	6	Jaundice	4	169	219	933	1470	330	20	Nil
4 (M, 55)	Skullcap; *Ginkgo biloba*	14	18	Jaundice; pruritus	5	181	150	1018	1293	373	7	Prednisone
5 (M, 25)	Chaparral;* dandelion; *Withania somnifera*; horsetail; echinacea	6	8	Jaundice; pruritus; fatigue	4	684	159	3910	3104	318	7	Prednisone
6 (F, 23)	Greater celandine;* buchus leaf; *Uva ursi*; juniper; parsley piert; choline bitartrate; dandelion	12	12	Jaundice; pruritus; fatigue	5	1073	134	2092	3764	81	25	Prednisone

* Herbal remedies reported as hepatotoxic (see Box 3). † Bilirubin normal range < 20 μmol/L. ‡ Alkaline phosphatase (ALP) normal range 40–250 U/L. § Aspartate aminotransferase (AST) normal range < 35 U/L. ¶ Alanine aminotransferase (ALT) normal range < 40 U/L. ** Gamma glutamyltransferase (GGT) normal range < 50 U/L. N/A = not available. Botanical names: Black cohosh, *Cimicifuga racemosa*; Skullcap, *Scutellaria lateriflora*; Valerian, *Valeriana officinalis*; Passionflower, *Passiflora incarnata*; Hops, *Humulus lupulus*; Chasteberry, *Vitex agnus-castus*; Chaparral, *Larrea tridentata*; Dandelion, *Taraxacum officinale*; Horsetail, *Equisetum arvense*; Greater celandine, *Chelidonium majus*; Juniper, *Juniperus communis.*

copper profiles were in keeping with an acute phase response. The alpha-1-antitrypsin level was normal in all patients. An endoscopic retrograde cholangiopancreatogram demonstrated a normal biliary tree in two patients with jaundice and cholestatic features. All patients had normal imaging of the liver by upper abdominal ultrasound or computed tomography examination.

Percutaneous liver biopsy was performed in five subjects with severe hepatitis, and the liver removed at transplantation (Patient 1) was available for study (Box 2). The biopsies were processed routinely, three sections were stained with haematoxylin–eosin, and additional sections were stained with haematoxylin–van Gieson. In all biopsies there was moderate to marked portal and lobular hepatitis. The limiting plates showed moderate to severe interface hepatitis (piecemeal necrosis). In addition, there was confluent zone 3 dropout and linkage of portal tracts and central veins. Eosinophils were present in five of the six cases but were not a conspicuous feature. All the biopsies were typical of acute hepatitis such as that seen in severe viral hepatitis. These changes are typically found in severe immunological reactions and are not the changes of direct toxic injury.

Three patients with persistent jaundice and severe pruritus were treated with oral prednisone, resulting in immediate improvement in the symptoms of pruritus and jaundice.

Discussion

Herbal remedies, like conventional medications, carry a risk of adverse reactions. There are many factors contributing to the potential toxicity of herbs. These include misidentification of the plant, variability in the time and place of collecting the plant, use of the wrong part of the plant, incorrect storage, contamination during preparation, and inconsistency in nomenclature and labelling of the final product.[10] Adulterants such as corticosteroids have been

2: Liver histology for the six patients*

Patient	Interface hepatitis (0–4)	Portal inflammation (0–4)	Zone 3 hepatocyte loss (0–4)	Bridging necrosis (0–2)	Lobular inflammation (0–4)	Eosinophils (0–2)	Bile duct damage	Fibrosis (0–6)
1	++	++	++++	++	++	++	0	Early
2	++++	++++	+++	focal	++++	++	0	0
3	+++	++	++++	+	++++	+	0	Early
4	+++	++	+++	focal	+++	0	0	0
5	+++	+++	+++	focal	++++	++	0	0
6	+++	+++	++++	+	++++	+	0	0

* Scoring system adapted from Ishak et al.[9] Eosinophils 0 = none; 1 = 1–4 per portal tract; 2 = > 4 per portal tract.

added to some preparations.[11] The remedies may have multiple ingredients, creating difficulty determining the causative agent and possible mechanism of injury. The identification of a herbal remedy as being responsible for hepatotoxicity often depends on demonstrating a temporal relationship between consumption of the product and development of the illness and improvement after discontinuation, after excluding other causes of liver disease.

Some herbal agents used as medicinal products which are known to cause liver disease are listed in Box 3. We have identified six patients who developed abnormal liver function tests after taking herbal remedies. Other causes of liver disease were excluded. One patient required urgent liver transplantation, and the others recovered after stopping the herbal remedy. For ethical reasons, challenge experiments were not performed. Liver biopsies were characteristic of an idiosyncratic, immunological reaction[24,25] and were very similar to the changes seen in acute viral hepatitis. In particular, there was prominent hepatocyte apoptosis, acinar zone 3 dropout, and at least focal bridging "necrosis" in all cases. This pattern of injury has been noted with skullcap and valerian,[19] but differs from the liver injury described with chaparral[12] and germander,[14] where true coagulative necrosis rather than apoptosis is observed (suggesting toxic injury and not an immunological reaction).

The most serious illness occurred in a 47-year-old woman (Patient 1) who was taking black cohosh for symptoms related to the menopause. Histological examination of her explant liver confirmed severe hepatitis and multiacinar dropout. The large number of synonyms for black cohosh highlights the problems with nomenclature, with up to 20 names used in North Carolina and South Carolina alone.[11] It is widely used, particularly in Europe, for its putative beneficial influence on perimenopausal symptoms.[26] In the United States, the Food and Drug Administration (FDA) lists it as a "herb of undefined safety".[27] There are no restrictions on the use of black cohosh in Australia. It contains a mixture of alkaloids, tannins and terpenoids, and has not previously been reported to have hepatotoxic effects. Diterpenoids have been shown in animal models to result in liver injury, either by reactive metabolites or by an autoimmune mechanism.[7]

Previous studies have incriminated mixtures of skullcap and valerian as causing hepatitis,[13,19] with jaundice and marked elevation in serum bilirubin and alanine aminotransferase levels being features. In our series, two patients (2 and 3) were using this combination and a further patient (4) used skullcap without valerian. In addition, the mixture Patient 2 took also contained black cohosh.

Patient 5 was taking a combination of herbs that included chaparral. Chaparral, when taken in capsule or tablet form, can cause subacute hepatitis, but no deaths have been reported.[12] In 1992, the FDA issued a warning about the potential danger of its use. There are no reported cases of the other herbs being hepatotoxic.

3: Common herbal remedies suspected of being hepatotoxic

Common name	Botanical name	Potential toxic constituents	Indications	Hepatic disease	References
Chaparral	*Larrea tridentata*	Nordihydroguaiaretic acid	Free radical scavenger Delays aging	Hepatitis	Gordon et al (1995)[12]
Comfrey	*Symphytum officinale*	Pyrrolizidine alkaloids	Herbal tea Poultice	Veno-occlusive disease Hepatic adenomas	Miskelly et al (1992)[13]
Germander	*Teucrium chamaedrys*	Furano neoclerodane Flavonoids	Antipyretic Weight control	Hepatitis	Larrey et al (1992)[14]
Greater celandine	*Chelidonium majus*	Unknown	Gallstones Dyspepsia	Hepatitis	Benninger et al (1999)[15]
Jin Bu Huan	*Lycopodium serratum*	Unknown	Sedative Analgesic	Hepatitis	Graham-Brown (1992)[16]
Kombucha tea	Kombucha "mushroom"	Unknown	Arthritis Cancer cure	Hepatitis	Perran et al (1995)[17]
Mistletoe	*Viscum album*	Unknown	Antihypertensive Sedative	Hepatitis	Harvey and Colin-Jones (1981)[18]
Mixtures of valerian and skullcap	*Valeriana officinalis* *Scutellaria lateriflora*	Alkylating agents Crystalline glycoside and a volatile oil	Sedative Sedative	Hepatitis Hepatitis	MacGregor et al (1989)[19] Miskelly et al (1992)[13]
Pennyroyal oil (squawmint oil)	*Labiatae* spp.	Pulegone	Abortifacient Menstrual complaints	Hepatic necrosis	Anderson et al (1996)[20]
Sassafras	*Sassafras albidum*	Safrole	Arthritis	Hepatitis Hepatocarcinogen	Segelman et al (1976)[21]
Senna	*Cassia angustfolia*	Sennosides	Laxative	Hepatitis	Beuers et al (1991)[22]
White chameleon	*Atractylis gummifera*	Potassium atractylate Gummiferin	Antipyretic Purgative	Hepatitis	Georgiou et al (1988)[23]

Patient 6 was taking a preparation containing a mixture of herbs advertised as a fat metaboliser and a fluid retention remedy. Greater celandine (*Chelidonium majus*) has been associated with acute hepatitis characterised by marked cholestasis.[15] Buchus leaf contains pulegone, a volatile oil also found in pennyroyal oil. Pulegone has been reported to be hepatotoxic,[28] either directly or via a reactive intermediate.[29]

The true incidence of hepatic damage caused by herbal medications remains unknown owing to a lack of prospective studies. The incidence of hepatotoxicity from Chinese herbal remedies has been estimated at between 0.2% and 1%.[30] With the increasing use of herbal remedies, medical practitioners need to be aware of the potential adverse effects and should routinely ask patients about all medications, including herbal mixtures. Labelling and advertising should include the known adverse effects, and a public education program is needed so that consumers are more aware of potential risks. The establishment of the Office of Complementary Medicine should address some of these issues. Finally, toxicity testing for plants and herbs used therapeutically should be undertaken as for manufactured drugs.

Competing interests

None identified.

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