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Hepatotoxicity Associated with Herbal Products

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A significant number of herbal products have been associated with hepatotoxicity. Unlike pharmaceutic products that undergo clinical trials before release to the public, herbal products have no preapproval evaluation time period in which liver injury may be identified. The association of hepatic injury with an herbal product is recognized only after numerous patients have contracted disease. This problem is confounded by the fact that less than 1% of the adverse events associated with dietary supplements are reported to the US Food and Drug Administration (FDA) [1]. Attribution of liver injury to a specific herbal product may be difficult. There are few clinical or laboratory manifestations that specifically suggest that liver injury is the result of a specific herbal. The most important clue often is the temporal relationship between initiation of the herbal product and the appearance of liver injury, and of equal importance is the resolution of the injury following withdrawal of the herbal product [2].

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Several factors may contribute to the hepatotoxic effects of herbal preparations. Foragers frequently misidentify plants, sometimes collecting toxic species. Seasonal variation of plant composition occurs; therefore the dosing of the biologic compounds received varies from product to product depending on the time of harvest and the part of the plant ingested. Common names often are applied to several different plants, confusing identification. Herbal preparations often contain multiple plant products or other compounds that may contribute to the hepatotoxicity [3]. Many herbal preparations used in North America are taken in addition to pharmaceutic products, and potential drug interactions may occur that have previously not been recognized. Contamination of products also has been reported. For example, Adachi and colleagues [4] reported 12 cases of N-nitroso-fenfluramine contamination of two popular herbal preparations in Japan, resulting in one liver transplant and one death.

Most of the medical literature addressing this problem exists in the form of case reports. There are few case control or cohort studies. For that reason, determination of relative toxicity is based on the number and strength of such reports. There are numerous herbal products that have been associated with hepatotoxicity (Box 1). This article reviews some of the herbal products more commonly associated with hepatotoxicity.

Box 1. Herbal products with reported hepatotoxicity

American Skullcap (*Scutellaria laterifolia*)
Cascara Sagrada (*Rhamnus purshiana*)
Chaparral (*Larrea*)
Comfrey (*Symphytum*)
Dog's tail (*Heliotropium angiospermum*)
Germander (*Teucrium chamaedrys*)
Greater celandine (*Chelidonium majus*)
Impila (*Callilepis laureola*)
Jin Bu Huan (*Stephania sinica*)
Kava (*Piper methysticum*)
Ma Huang (*Ephedra*)
Margosa oil (*Melia azadirachta*)
Mistletoe (*Phoradendron serotinum*)
Pennyroyal (*Mentha pulegium* or *Hedeoma*)
Rattlebox (*Crotalaria*)
Sassafras Oil (*Sassafras*)
Senecio (*Senecio aconitifolius*)
Senna (*Cassia acutifolia*)
Valerian (*Valeriana officinalis*)
White Chameleon (*Atractylis gummifera*)

Pyrrolizidine alkaloids

The hepatotoxic effects of the pyrrolizidine alkaloids (PAs) are well documented. Early reports began in 1920 when Wilmont and Robertson [5] described five patients with acute hepatic failure. The investigators noted that several families in South Africa were struck by this disease, which resembled similar conditions in livestock. This finding suggested that a dietary exposure was occurring. It had been demonstrated that *Senecio ilicifolius* and *S burchelli* ingestion were responsible for such symptoms in cattle, and on further inspection those plants were found to contaminate poorly winnowed wheat. In 1951, Selzer and Parker [6] reported unique clinical features of 12 patients and six autopsy results in Cape Town, South Africa. They described rapid onset of ascites, hepatomegaly, nausea, and vomiting coupled with autopsy findings consistent with Chiari's syndrome. In 1954, Bras and colleagues [7] reported comparable cases from Jamaica loosely linked with the consumption of bush tea. Similar reports subsequently arose from Egypt, India [8], Afghanistan [9], Great Britain [10], and the United States [11–14]. By the 1980s, the PAs contained within these plants had been identified as the cause. These plants come from the genera Senecio, Crotalaria, Heliotropium, and Symphytum [15]. PAs had contaminated herbal teas, flour, and cereals.

PAs are distributed widely and found in approximately 3% of the world's plants. Approximately 300 compounds with similar structures have been identified and their toxicity varies widely. The basic structure of PAs is the necine base, as shown in Fig. 1. Toxicity is determined by alterations of that base. Characteristics that result in enhancement of toxicity include

Double bond of the 1,2 position of the unsaturated necine base
Esterification of hydroxyls at 7 and 9
Branched carbon chain in the ester side chains

The PAs are metabolized by way of three pathways. They are hydrolyzed to form necine bases then either oxidized to form innocuous N-oxides or hydroxylated and dehydrated by way of cytochrome p450 (3A4 and 2B6) to

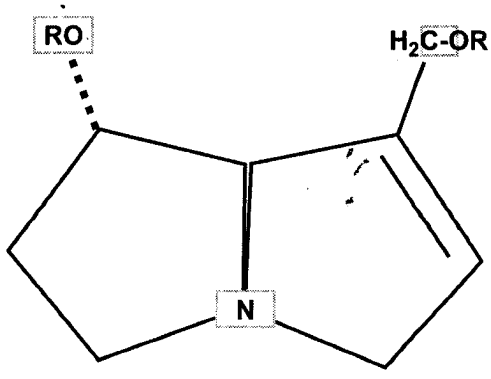

Fig. 1. Pyrrolizidine alkaloid structure.

form pyrroles [16]. Pyrroles act as alkylating agents capable of inducing hepatocellular injury. Compounds capable of inducing 3A4 metabolism, such as phenobarbital, can increase pyrrole production, whereas 3A4 blockers reduce it. Pyrroles damage the sinusoidal endothelium causing the extravasation of red blood cells into the space of Disse. As a result, reticulin fibers are generated in the lumen of central and sublobular veins obstructing venous flow and causing hepatic congestion that ultimately results in hepatic necrosis [16]. The resultant clinical presentation is that of abdominal pain, hepatomegaly, and ascites.

Animal studies have demonstrated genotoxicity, including DNA binding, cross-linking, mutagenicity, and carcinogenicity. Carcinogenicity has yet to be demonstrated in humans.

Infants appear to be most susceptible to PA-induced toxicity. The acute syndrome presents with abdominal pain and sudden-onset ascites. Cirrhosis and portal hypertension also may occur. Death reportedly occurs in approximately 20% of acute cases, though the exact prevalence is not known [17]. A chronic form of toxicity also has been reported that begins with weakness and diarrhea. Portal hypertension also may occur and can progress to esophageal varices, encephalopathy, and death. The overall mortality of both syndromes is 40% [16,18,19]. PAs also have been shown to cause a veno-occlusive pulmonary disease in animals, but that has not been reported in humans with PA exposure [20].

Diagnosis usually is established by liver biopsy. Detection of PAs by high performance liquid chromatography or gas chromatograph-mass spectroscopy is of little clinical value. Aspartate aminotransaminase, gamma-glutamyltransferase, and bilirubin frequently are elevated, but not always [21].

The treatment of PA toxicity essentially is the same as treatment of veno-occlusive liver disease. Supportive care is focused on limiting exposure to hepatotoxins and nephrotoxins while reducing sodium and fluid load. Reversal of coagulopathy and reduction of ascites with paracentesis are also important. N-acetylcysteine has been used successfully in animals, but its benefit is not proven in humans [16]. Defibrotide has been shown to modulate endothelial cell injury without increasing hemorrhage [22]. Patients presenting with multiorgan failure have a poor prognosis [23].

Liver transplant is an option. In those able to undergo the procedure, about 30% experience clinical improvement [23]. Transjugular intrahepatic portosystemic shunts have been of benefit in veno-occlusive disease and may be a consideration in appropriate candidates [24].

At autopsy, the liver commonly demonstrates a fine granular cirrhosis with a nutmeg appearance secondary to chronic passive congestion. Small and medium-sized branches of the hepatic vein commonly show wall thickening, but larger veins often are spared. Affected vessels are surrounded by fibrosis. There often is coalescence and marked widening of sinusoids in central lobular areas. Obliteration of hepatic vein radicals has been remarkable in some cases. Central veins often are unrecognizable. There are varying

amounts of subendothelial swelling with concentric swelling of the intima that begins with fibrin formation, then reticulin, collagen, and elastic tissue, and finally irregular swelling suggesting organized thrombus. Fibrosis begins in nonportal areas, but progresses to portal areas in the final stages [7,9].

Germander

Germander *(Teucrium chamaedrys)* has been advocated for the treatment of gout, obesity, diabetes mellitus, diarrhea, and fever. In 1986, France approved the marketing of the use of Germander. By 1992, several reports of hepatitis had surfaced in connection with its use [25,26]. Most cases involved women taking the product for weight loss in doses of 600 to 1600 mg per day for 2 or more months. Acute cholestatic hepatitis was the most common presentation with some patients developing cirrhosis. Those who did not develop cirrhosis recovered on discontinuation of the drug. Germander initially was not identified as the hepatotoxin until a patient who was accidentally re-exposed developed hepatitis [17]. In a subsequent series, 12 of 26 patients re-exposed to Germander redeveloped evidence of hepatitis [27]. Other *Teucrium* species also have been associated with hepatitis and liver failure [27–29].

Teucrium species contain glycosides, saponins, and flavonoids. Furano neoclerodane diterpenoids, namely teucrin A and teuchamaedryn A, however, are considered the responsible toxic components. Other diterpenoids also have been discovered. By way of oxidation by CYP3A4, the furan ring of these diterpenoids is converted to an epoxide that can react with CYP3A and epoxide hydrolase. Animal studies have indicated that the epoxide also can change mitochondrial permeability, activate caspase, and increase apoptosis. The epoxide can decrease hepatocyte glutathione. This activity results in plasma membrane blebs, DNA fragmentation, and cell apoptosis. Further study has indicated that glutathione depletion increased hepatocyte damage, whereas glutathione replacement decreased it. An immune cause also has been suggested. When the epoxide binds to epoxide hydrolase on the surface of the hepatocytes, autoantibody formation may lead to an immune response resulting in cell death [30].

Clinically, case reports have described a gradual onset of malaise, anorexia, and jaundice similar to acute hepatitis. Patients usually seek medical attention after noting change in skin or urine color. Elevation of conjugated bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and alkaline phosphatase are common. Antinuclear antibodies, antimitochondrial antibodies, and anti-smooth muscle antibodies have been reported positive [28,29]. *T spp* have been identified by gas chromatography-mass spectrometry [31] and high performance liquid chromatography [32]. Biopsies demonstrated hepatocyte necrosis and polymorphonuclear and mononuclear infiltration of the centrilobular area. Inflammatory cells were identified in the portal tracts [25].

Treatment is supportive and most cases have resolution of hepatitis after discontinuation of the supplement. Patients should be warned against its resumption.

Chaparral

Chaparral *(Larrea tridentata)* commonly is called creosote bush or greasewood. It is a desert shrub ubiquitous in the Southwest. Because it has a woody stem it technically is not an herb but commonly is regarded as one. Chaparral, made from the leaves of *L tridentata*, has been advocated for the treatment of colds, infertility, rheumatism, arthritis, diabetes, gallstones, kidney stones, and snake bites. It also is recommended as an antioxidant. Currently it is sold as a tablet or salve.

Sheikh and colleagues [33] in 1997 reviewed 13 case reports of hepatotoxicity that had occurred since 1990. They found that onset of symptoms ranged from 3 to 52 weeks from the onset of use. Although most clinical effects had resolved by 17 weeks following cessation of use, four patients progressed to cirrhosis with two requiring liver transplantation. Other cases have been reported [34,35], including one in which rechallenge resulted in return of hepatic injury [35]. In that case, the patient presented with jaundice, malaise, and elevation of transaminases and bilirubin. Her use of chaparral was unknown at that time. She had taken chaparral for 8 weeks before her first presentation, was off the compound during hospitalization, but began taking it again on discharge. She returned for readmission after 11 days of twice daily dosing [35]. The authors were criticized, however, because they failed to confirm that the causative agent in question was in fact *L tridentata.*

The mechanism of hepatotoxicity is not known definitively; however, one component has gained significant study. Nordihydroguaiaretic acid (NDGA) is a lignan that has been identified as hepatotoxin in mice. It is found in the leaves and bark of *L tridentata* and constitutes up to 10% by dry weight. It seems to be detoxified by glucuronidation. NDGA is an antioxidant. In low doses it inhibits lipoxygenase pathways and at higher concentrations it also inhibits cyclo-oxygenase pathways. It is a cytochrome p450 inhibitor in rats. One hypothesis is that at high concentrations capable of cyclo-oxygenase inhibition NDGA could favor proinflammatory mediators leading to hepatotoxicity [36].

The possibility of an immune-mediated event is particularly inviting because hepatitis only occurs rarely. The onset seems to require 2 or more months of therapeutic dosing but is variable. Though cessation of chaparral usually leads to resolution, rechallenge causes a much more rapid relapse [35].

Most reports document patients presenting with fatigue, dark urine, jaundice, right upper quadrant abdominal pain, nausea, and diarrhea. Some patients develop weight loss, pruritus, anorexia, and fever [33]. A few progress

to severe hepatitis and hepatic failure [36]. Renal failure has been reported in a patient requiring liver transplant [36]. It is difficult to determine if this has a direct link to the ingestion of chaparral. Cystic renal disease has been reported in rats and one case with renal cell carcinoma has been reported in a chronic chaparral user [37]. Laboratory testing demonstrates an increase in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma-glutamyltransferase, and prothrombin time. Albumin may be decreased [33,36]. Biopsy shows hepatitis with lobular collapse, nodular regeneration, mixed portal inflammation, and bile duct proliferation [36]. Treatment is supportive following withdrawal from the exposure.

Impila and white chameleon

Impila, a product from *Callilepis laureola,* is used for stomach problems, impotence, cough, and tapeworm infestations. Its use primarily occurs in Africa, especially among the Zulu. Its toxicity has been recognized since the early 1900s but its use has continued to the present day. It is estimated that 1500 people die yearly in a single South African province as a result of impila toxicity [38]; however, this may be an overestimation [39]. The plant, a member of the Compositae family, is related to the daisy and sunflower. Its tuberous root is the source of impila. It is dried and pulverized. The powder is then boiled in water and taken orally or as an enema. Toxicity may be dose dependent. Despite numerous cases of hepatotoxicity and death, it continues to be a popular herbal preparation. Deaths more commonly occur in children less than 10 years old. In patients with severe toxicity, the death rate is estimated to be 63% in the first 24 hours and 91% overall.

White chameleon, Mediterranean thistle, or Daad, is made from *Atractylis gummifera,* a low-growing thistle. Its toxicity was first described in the mid-1800s [40]. About 100 cases have been reported since. *A gummifera* has toxicity similar to that of *C laureola.* Carboxyatractyloside (CATR) and atractyloside (ATR) have been extracted from the plant.

CATR is a glycoside found in the tuber. It decomposes to ATR. The latter has been found in other plants of Africa, Europe, Asia, and South America, including the Mediterranean thistle (*A gummifera*). Another ATR-containing plant, *Xanthium strumarium*, or cocklebur, is known to cause central lobular necrosis in livestock and recently has been reported to cause hepatic damage, renal toxicity, and death in humans [41]. *X strumarium* is a common plant in the United States, with worldwide distribution.

CATR and ATR inhibit the transport of ADP across the mitochondrial membrane reducing ATP production and leading to cell death. As a result of CATR and ATR activity, mitochondrial permeability transition pores open causing the release of cytochrome c and other proteins from the intermembranous space into the cytoplasm. This phenomenon contributes to condensation of chromatin and formation of ladder DNA associated with

apoptosis. Nephrotoxicity has been linked with ATR, but not CATR. ATR may also destroy tubulin, interfering with microtubule construction necessary for mitosis [42].

Onset of clinical findings reportedly is abrupt, with vomiting, abdominal pain, and diarrhea. Hepatic and renal failure lead to profound hypoglycemia, encephalopathy, convulsions, and frequently death.

Wainwright and Schonland [43] reported that the liver appeared pale and yellow without signs of congestion with sharp demarcation of centrilobular, punctate areas of congestion giving it a speckled appearance. The weight of the liver was reduced in 50% of cases, but renal weight was increased in 70%. The kidney demonstrated evidence of tubular necrosis involving convoluted tubules and loops of Henle. There were hyaline, granular, and red cell casts in the tubules. Interstitial edema and tubulovenous aneurysms occasionally were seen [43]. Although no specific therapy exists, there has been interest in the development of Fab-specific fragments [44,45].

Margosa oil

Margosa oil is extracted from the seeds of the neem tree *(Azadirachta indica)* commonly found in India, Pakistan, and the West Indies. Its fruit is toxic. It is used as a therapy for various skin diseases and otitis. Although intended for topical use, it is sometimes given orally and has been reported to cause a Reye-like syndrome in humans [46–48] and animals [49].

Although the mechanism of toxicity has not been defined clearly, it seems that margosa oil targets mitochondria by uncoupling oxidative phosphorylation and reducing ATP production [50].

In reports of childhood exposure, the amount of ingestion varied from a few drops to 12 mL on 2 successive days. Vomiting, loss of consciousness, and convulsions were reported. Transaminases were mildly elevated [46,48,50]. One child died [48]. Autopsy revealed hepatic edema without necrosis or inflammation. Cerebral edema was present. Electron micrographs demonstrated fatty vacuolation of hepatocytes with increased peroxisomes, flocculation of mitochondria, and marked proliferation of smooth endoplasmic reticulum.

Treatment is supportive. There is some evidence that carnitine and glucose may be of benefit [51].

Kava

Kava (*Piper methysticum*) is a perennial plant that has been used by South Pacific Islanders for centuries as part of spiritual services and as a ceremonial intoxicating beverage [52]. Kava has been advocated as a sedative, anxiolytic, anesthetic, muscle relaxant, and anticonvulsant [53–55]. Numerous reports have arisen demonstrating a relationship between kava ingestion and liver toxicity [56–58]. In November of 2001, European country

regulatory authorities placed restrictions on the sale of herbal products containing kava [59]. The United Kingdom and Canada have banned kava sales [60,61]. In the United States, kava still is used by many health enthusiasts, despite warnings issued by the FDA regarding its safety [59,62,63].

Kava extract's bioactivity most likely is because of the presence of kavalactones (also known as kava pyrones). Numerous kavalactones have been isolated and include yangonin, desmethoxyyangonin, kavain, dihydrokavain, methysticin, and dihydromethysticin [64]. Peak plasma levels of kavalactones occur within 2 hours of ingestion; elimination of the parent compound and the metabolites occurs in the urine and feces, and their elimination half-life is approximately 9 hours.

Kava-induced hepatotoxicity possibly is related to the extraction method of kavalactones from the roots of the plants [65]. The traditional kava extracts are prepared by maceration of the roots in a water and coconut milk solution [54]. Commercial extracts commonly use either an ethanol, methanol, or an acetone as extraction solvents. It has been hypothesized that the Pacific extraction methods may remove more toxic components from the plant and contain less kavalactones [52,55]. In one study the traditional water-extraction product contained approximately 30% kavalactones, whereas the acetone-extraction product contained up to 70% kavalactones. Lower levels of kavalactones and higher variations were observed in tea bags from water extraction as compared with methanol extraction [64]. Other studies have documented that there is little difference between aqueous and acetonic and ethanolic extract content [66]. Some products have synthetic kavain added to increase the biologic activity of the extract and thus may increase further the potential for toxicity [67].

The definitive mechanism of liver injury associated with kava consumption is not known and may involve a metabolic and or an allergenic idiosyncrasy. There have been several hypotheses as to the cause of hepatotoxicity associated with kava consumption. First, kavalactones inhibit cytochrome P450 activity. Significant inhibition of CYP1A2, 2C9/19, 2D6, 3A4, and 4A9/11 has been demonstrated under experimental conditions [61,68]. It is hypothesized that those of European decent may be at more risk for inhibition because of the 7% to 9% incidence of CYP2D6 deficiency in such groups. This deficiency is rare in the South Pacific and may be one reason for the lack of reported toxicity in this population [69]. Case reports of kava-induced liver dysfunction have not demonstrated CYP2D6-poor metabolizer status [70]. Second, kavalactones inhibit cyclooxygenase enzymes (COX-1 and COX-2) [71]. COX-2 serves an important hepato-protective function and COX inhibition may contribute to the risk for kava-induced liver injury [72]. Third, kava induces glutathione depletion [67]. It has been hypothesized that kava has the potential to saturate enzymatic detoxification pathways that use glutathione and therefore place undue stress on the liver [61]. Kava products with high content of kavalactones have the potential to deplete glutathione stores markedly.

In native South Pacific kava consumers, gamma-glutamyltransferase levels have been found to be elevated, but no cases of acute liver injury have been identified [70,73]. The gamma-glutamyltransferase elevation is reversible and returns to baseline within 2 weeks of kava discontinuation [74]. This increased activity of gamma-glutamyltransferase in heavy kava consumers in the presence of normal or minimally elevated transaminases is probably not a sign of liver injury but rather reflects an induction of CYP450 enzymes [70].

Two patients, aged 59 and 55, presented with acute hepatitis associated with consumption of traditional aqueous kava extract [70]. Both patients presented with jaundice, elevated liver transferases, and elevated total bilirubin, with one patient also presenting with a prolonged thromboplastin time and eosinophilia. Symptoms developed 4 to 5 weeks after starting to drink kava with laboratory values normalizing within 3 months of ceasing kava consumption.

A 14-year-old girl developed fulminant hepatic failure requiring liver transplantation following ingestion of a kava-containing product for 4 months. No other causes of liver failure could be found. The patient's liver biopsy before transplant demonstrated hepatocellular necrosis consistent with chemical hepatitis [75]. In another report, a 39-year-old woman presented with a history of elevated liver enzyme levels following chronic ingestion of kava. One week after discontinuation of all medications, the patient's transaminases normalized. Two weeks after rechallenge with kava, her liver enzyme levels again became elevated. A liver biopsy revealed acute necrotizing hepatitis. Kava was again discontinued and the patient's transaminase levels returned to normal [76].

In a retrospective review of published (n = 7) and unpublished (n = 29) cases of kava-associated hepatotoxicity reported to the German Federal Institute for Drugs and Medical Devices between 1990 and 2002, the most frequent liver injuries were hepatic necrosis (n = 16), cholestatic hepatitis (n = 7), and lobular hepatitis (n = 1). Fulminant hepatic failure was reported in nine patients, three of whom eventually died. Of the nine patients with fulminant hepatic failure, eight underwent liver transplantation [58].

Pennyroyal

Pennyroyal oil is an herbal product that has been purported to treat upper respiratory tract and ear infections, induce abortions, and act as an insect repellent [77–79]. Although these claims are suspect, pennyroyal oil's inherent toxicity is not. The pure oil is derived from the *Mentha pulegium* and *Hedeoma pulegoides* plant species. It is available readily commercially and has a characteristic mint-like odor [78].

Pennyroyal's primary chemical component, pulegone, is metabolized by the liver using the cytochrome P450 system to menthofuran, a directly

hepatotoxic metabolite [80]. Furthermore, in a manner apparently independent of menthofuran, pulegone causes depletion of glutathione stores [81]. Without adequate glutathione stores menthofuran and other toxic metabolites increase in concentration and hepatotoxicity is accentuated [77,80–83]. Subsequently, patients who ingest pennyroyal oil may develop hypoglycemia, elevated liver function tests, hyperbilirubinemia, hyperammonemia, and an elevated anion gap metabolic acidosis. Other clinical effects that may develop include nausea, vomiting, abdominal pain, gastrointestinal bleeding, renal failure, pulmonary edema, coagulopathy, disseminated intravascular coagulation, dizziness, weakness, syncope, mental status changes, and seizures [77,82,83].

In some reports of pennyroyal oil toxicity, small doses have resulted in serious toxicity with one source reporting as little as 10 to 15 mL of pure pennyroyal oil causing death [77]. There are reports describing coma and seizures with doses as low as one teaspoon (5 mL).

Animal studies have demonstrated pennyroyal-induced cellular necrosis in the centrilobular regions of the liver [80]. Pennyroyal-induced hepatitis, hepatocellular necrosis, and hepatic failure requiring transplant have been reported by multiple authors [77,82]. Bakerink and colleagues [83] reported the presence of hypoglycemia and elevated liver enzymes in two infant boys, an 8-week-old and a 6-month-old, following pennyroyal oil poisoning. The autopsy of the 8-week-old boy revealed confluent hepatocellular necrosis.

Treatment of pennyroyal oil toxicity begins with good supportive care. Prompt administration of *N*-acetylcysteine has been advocated to reduce the degree of liver injury [77].

Summary

A significant number of herbal products have been associated with hepatotoxicity. There are few clinical or laboratory manifestations that suggest specifically that liver injury is the result of a specific herbal. Compounding this difficulty is that the patient may have liver disease from another cause, may be taking other potentially hepatotoxic products, or may be taking a contaminated herbal product. Clinicians should consider herbal products in the differential diagnosis when evaluating patients with new-onset hepatotoxicity.

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