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Review article: herbal and dietary supplement hepatotoxicity

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SUMMARY

Background
Herbal and dietary supplements are commonly used throughout the World. There is a tendency for underreporting their ingestion by patients and the magnitude of their use is underrecognised by Physicians. Herbal hepatotoxicity is not uncommonly encountered, but the precise incidence and manifestations have not been well characterised.

Aims
To review the epidemiology, presentation and diagnosis of herbal hepatotoxicity. This review will mainly discuss single ingredients and complex mixtures of herbs marketed under a single label.

Methods
A Medline search was undertaken to identify relevant literature using search terms including 'herbal', 'herbs', 'dietary supplement', 'liver injury', 'hepatitis' and 'hepatotoxicity'. Furthermore, we scanned the reference lists of the primary and review articles to identify publications not retrieved by electronic searches.

Results
The incidence rates of herbal hepatotoxicity are largely unknown. The clinical presentation and severity can be highly variable, ranging from mild hepatitis to acute hepatic failure requiring transplantation. Scoring systems for the causality assessment of drug-induced liver injury may be helpful, but have not been validated for herbal hepatotoxicity. Hepatotoxicity features of commonly used herbal products, such as Ayurvedic and Chinese herbs, black cohosh, chaparral, germander, greater celandine, green tea, Herbalife, Hydroxycut, kava, pennyroyal, pyrrolizidine alkaloids, skullcap, and usnic acid, have been individually reviewed. Furthermore, clinically significant herb–drug interactions are also discussed.

Conclusions
A number of herbal medicinal products are associated with a spectrum of hepatotoxicity events. Advances in the understanding of the pathogenesis and the risks involved are needed to improve herbal medicine safety.

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INTRODUCTION

With historical background on use, the use of herbal medicine can be traced back as far as 2100 BC in ancient China and India.[1] Despite their largely unproven therapeutic potential through systematic and rigorous investigations, herbal therapy has been increasingly used for the treatment of various diseases, not only in the Eastern World but also in the Western World. In the US, herbal and dietary supplements (HDS) represent a $180 billion market and their use was reported by 18.9% individuals in 2004, and this had doubled from the previous decade.[2, 3] Interestingly, 30–40% of patients admitted that they did not disclose the use of HDS to their Physicians.[3] The list of the ten most commonly used herbal preparations for various conditions, included echinacea, garlic, ginko biloba, saw palmetto, ginseng, grape seed extract, green tea, St. John's wort, bilberry and aloe.[4] Notably, the use of HDS is particularly common in individuals with chronic liver disease, as was reported by 30–62% of patients who ingested silymarin (milk thistle).[3] This population is theoretically more susceptible for hepatotoxicity as well as more likely to develop severe hepatic adverse consequences.

HERBAL PRODUCTS AND THEIR REGULATIONS

Herbal products used for treating disease exist as both crude and commercial preparations. Crude herbal products (come as roots, leaves, seeds or teas) are more often used in less developed countries. They are sometimes formulated as a mixture (i.e. Chinese and Thai herbal medicine, and Indian ayurvedic medicine), where often all constituents are not known and may contain harmful contaminants, such as heavy metals (i.e. lead, mercury and arsenic), corticosteroids nonsteroidal anti-inflammatory drugs and benzodiazepines.[5] Commercial herbal products (as tablets or capsules) are more commonly used in developed countries. They often vary in content and concentration of chemical constituents from batch-to-batch and also come from different manufacturers. Even with standardisation for the known active compounds, there may be variation in other constituents, resulting in differences in bioavailability and pharmacological activity in humans.[2, 5, 6] In the US, these commercial herbal products are expected to adhere to the regulations of the Dietary Supplement and Health Education Act (DSHEA), issued in 1994, and the Final Rule for Current Good Manufacturing Practices for Dietary Supplements, issued in 2007. These regulations require for the manufacturers to determine the safety of herbal products before marketing, to define dietary ingredients as vitamins, minerals, herbs, amino acids (and any concentrate, metabolite, extract thereof), to provide standards in identification and purity and as well as to ensure that claims made regarding the product are accurate and not misleading.[2, 5] However, this does not always guarantee good manufacturing practices and the manufacturers are not bound to register their products before distribution.[2, 5] Thus, there is no aspect of the law to give the US Food and Drug Administration (FDA) authority to review and approve herbal products for safety and effectiveness.[2]

EPIDEMIOLOGY

The true prevalence of herbal product use and incidence of herbal hepatotoxicity are unknown. Unlike modern prescription medications, current regulations for herbal products do not mandate systematic surveillance or reporting of adverse events by the manufacturer to the FDA. Therefore, the data regarding herbal hepatotoxicity are derived largely from anecdotal case reports, case series, retrospective databases and, more recently, from prospective registries of drug-induced liver injury (DILI), such as the US DILI Network and the Spanish DILI Registry. Notably, some of these DILI reports have excluded patients with herbal hepatotoxicity. Based on available data of DILI cohorts from the US and Europe, herbal products are implicated as a cause of hepatotoxicity in 2–11% of patients with DILI,[7–9] and in 5–10% of patients with drug-induced acute liver failure (ALF),[10, 11] although a single-centre experience has implicated HDS in up to 70% of patients with ALF.[12] These numbers reflect the magnitude of herbal hepatotoxicity in clinical practice, and it should again be emphasised that this prevalence is likely to be underestimated. As traditional herbal medications are widely used in China and India, as well as in many other countries in Southeast Asia, Africa and Central America, one can speculate that herbal hepatotoxicity is encountered commonly in these parts of the World. While the data from such areas are scant, prospective DILI studies from Korea and Singapore do support this assumption by reporting a high prevalence of herbal hepatotoxicity, among all cases of DILI, of 73% and 71% respectively.[13, 14] Surprisingly, a low prevalence of herbal hepatotoxicity (1.3%) was reported from India, where the use of herbal remedies and ayurvedic compounds are quite common.[15] Although the exact reasons remain unclear, the authors speculated that ayurvedic compounds in India are often taken after the development of a hepatitis like illness and the high rate of heavy metal contamination in the

remedies result in a more dominant nonhepatic organ involvement that may overshadow hepatitis, which may be insignificant and overlooked and thus, underreported[15] (Table 1).

The incidence of idiosyncratic liver injury among persons who use HDS is variable. Based on limited data, the incidence of hepatotoxicity from Chinese herbs appears to be low (less than 1%).[16, 17] Melchart *et al.* reported a study of 1507 consecutive inpatients treated with traditional Chinese medicine wherein 1% developed more than 2-fold elevation of serum alanine aminotransferase (ALT), and only 2 patients were symptomatic.[16] Furthermore, a prospective, observational study from Korea reported that significant changes in hepatic biochemical tests were not observed among 122 patients who took herbal medicine.[17] However, relatively high incidence of hepatotoxicity has been reported in a randomised controlled trial of *Tinospora crispa* as an adjunctive therapy for diabetes mellitus ($N = 40$), wherein significant ALT elevations (>200 IU/L) occurred in 10% of patients.[18] Although it is difficult to quantitate the exact amount of active herbal ingredients ingested, dose-dependent pattern of hepatotoxicity can be seen with several herbs, such as pyrrolizidine alkaloids (PA), greater celandine and *Atractylis gummifera*.

Table 1 | Herbal and dietary supplement hepatotoxicity: Prevalence and clinical features among drug-induced liver injury in different reports

Reference	Countries and patient characteristics	Prevalence of HDS hepatotoxicity	Clinical features and prognosis of cases identified as HDS hepatotoxicity
Ibunez *et al.*[9]	Spain (1993–1998) *N* = 103; DILI Population-based, prospective	11%	64% hepatocellular injury 18% mixed injury 18% cholestasis injury
Andrade *et al.*[7]	Spain (1994–2004) *N* = 446; DILI Multi-centre, prospective	2%	89% hepatocellular 11% cholestasis 56% needed hospitalisation 11% death
Chalasani *et al.*[8]	USA (2003–2008) *N* = 300; DILI Multi-centre, prospective	9%	63% hepatocellular 17% cholestasis 21% mixed injury 41% needed hospitalisation 6% ALF 9% chronic DILI
Suk *et al.*[13]	Korea (2005–2007) *N* = 371; DILI Multi-centre, prospective	73% (40% herbs, 14% dietary supplement, 19% folk remedies)	~78% hepatocellular ~10% cholestasis ~12% mixed injury 1.5% death or LT
Wai *et al.*[14]	Singapore (2004–2006) *N* = 31; DILI Multi-centre, prospective	71%	74% hepatocellular 19% cholestasis 7% mixed injury
Devarbhavi *et al.*[15]	India (1997–2008) *N* = 313; DILI Single-centre, retrospective	1.3%	50% mortality
Estes *et al.*[12]	USA (2001–2002) *N* = 20, ALF Single-centre, retrospective	50%	60% underwent LT
Russo *et al.*[11]	USA (1990–2002) *N* = 270; ALF from drug Retrospective, UNOS data	5.1%	All underwent LT
Reuben *et al.*[10]	USA (1998–2007) *N* = 133; ALF from drug Multi-centre, prospective	10%	>90% hepatocellular injury 21% spontaneous recovery 50% underwent LT 29% death

ALF, acute liver failure; DILI, drug-induced liver injury; HDS, herbal and dietary supplement; LT, liver transplantation; UNOS, United Network for Organ Sharing.

PRESENTATION

The clinical presentation of herbal hepatotoxicity varies from asymptomatic abnormal hepatic biochemical test abnormalities indicating mild self-limiting liver injury, to severe ALF requiring LT. In symptomatic individuals, the manifestation often begins with nonspecific constitutional symptoms, followed by jaundice.[19] Due to the variety and complexity of herbal regimens, it is difficult to summarise the clinical manifestations of herbal hepatotoxicity in general. In 28 patients with DILI from herbs and dietary supplements in the US DILI Network, the median duration from exposure to DILI recognition was 54 days (IQR 36–109); 50% were female and the mean age was 45 (±12) years. Pattern of liver injury was hepatocellular in 63%, cholestatic in 17% and 21% were mixed, with a mean bilirubin of 14.7 (±13.0) mg/dL. The severity was mild–moderate in 88% of patients, whereas 12% have severe–fatal DILI; 3.5% of patients underwent LT and chronic DILI developed in 9%.[8] A prospective nationwide study of DILI in Korea reported 270 patients with HDS-related hepatotoxicity; most patients were female with median age of 48–53 years.[13] Hepatocellular pattern of injury was noted in the majority of cases (~78%) with a median ALT of 566–796 IU/L and a median bilirubin of 5.4–7.0 mg/dL. Median hospital stay was 7–9 days; most patients spontaneously recovered with 2 deaths and 2 requiring LT.[13]

DIAGNOSIS AND CAUSALITY ASSESSMENT

As with DILI, an early and high-index of suspicion of herbal hepatotoxicity is paramount. The use of herbal products should always be a part of history taking in patients presenting with any form of acute liver injury or in those with acute on chronic liver disease. Further details on all herbal preparations used, dose and duration and concomitant medications are essential. In some instances, it can be helpful to examine the label of the herbal products, which sometimes contains a long list of ingredients mixed in the preparation. Prompt recognition of common culprit herbs and their hepatotoxicity patterns (some of them may have a 'signature') reported previously in the literature (see below) is very important. Currently, there is no gold standard, even with a liver biopsy, for the diagnosis of herbal hepatotoxicity. The diagnosis, therefore, depends greatly on the exclusion of other causes of liver disease by a thorough clinical assessment, as well as laboratory testing. A list of essential diagnostic elements for the exclusion of other causes of hepatic dysfunction and to increase the reliability of the diagnosis of DILI has been suggested and this could increase the quality and clinical utility of the publications on drug toxicity.[20] Acute hepatitis E has accounted for some cases of suspected DILI (up to 13% in developed countries, and possibly much higher in developing countries),[21, 22] and therefore testing for hepatitis E antibody should be performed, particularity if clinical features resemble acute viral hepatitis.[22] The possibility of herbal hepatotoxicity superimposed on pre-existing liver disease should also be considered, especially because many herbal remedies are used by patients with chronic liver diseases, and in this situation, it is more challenging to make a clear-cut diagnosis. Liver histology often is nonspecific, but may be helpful in some cases. Uncommon histological patterns of liver injury should trigger the suspicion of herbal hepatotoxicity, and these include zonal necrosis, necrotic lesions with steatosis or bile duct injury, and vascular injury, particularly veno-occlusive disease (VOD).[19]

Several scoring systems have been proposed for aiding in the causality assessment of DILI, such as the Roussel Uclaf Causality Assessment Method (RUCAM) by the Council for the International Organization of Medical Sciences (CIOMS)[23] and the clinical scale by Maria and Victorino.[24] Among these scoring systems, the CIOMS scale is perhaps the most widely used in the literature.[8, 23] This scale applies numerical weighting to key features in 7 different domains: chronology (latency and dechallenge), risk factors, concomitant drug use, exclusion of other causes, previous information on drug's hepatotoxicity potential and response to rechallenge. The score given to each domain is summed up to generate a total score that reflects the causality probability of DILI; definite, very likely, probable, possible, unlikely or excluded.[23] The CIOMS scale, when initially validated, demonstrated acceptable reproducibility and performance, with 93% positive predictive value and 78% negative predictive value.[25] However, subsequent validations have questioned the reliability of this method, and there have been several pitfalls in applying the score in clinical practice.[26, 27]

Although the CIOMS scale has been utilised as a diagnostic tool in most of the literature pertaining to herbal hepatotoxicity, the performance of this method in causality assessment of herbal hepatotoxicity remains undefined. Herbals and dietary supplements are less likely to be well characterised with regard to hepatotoxicity information of the active ingredients. This may compromise the CIOMS score for herbal products as no points are given for agents without existing information on hepatotoxicity. A recent study from Hong Kong Herb-induced

Liver Injury Network evaluated the performance of CIOMS scale and a multidisciplinary approach (consisting of expert opinion by a hepatologist, clinical toxicologist, analytic toxicologist and Chinese medicine pharmacist) in 27 patients with suspected herbal hepatotoxicity. The concordance for causality assessment was moderate, either between the hepatologist and clinical toxicologist (weight k = 0.48), or between the multidisciplinary team and the CIOMS scale (weight k = 0.51).[28] The diagnostic algorithm for the causality assessment of drugs and dietary supplements, consisting of a pretest (qualitatively oriented for hepatocellular injury and/or cholestasis), a main-test (CIOMS scale) and a posttest (exclusion of other liver diseases not considered in the CIOMS) procedure, has also been proposed by Teschke.[29] More recently, a group of experts from the US DILI Network has developed a novel causality assessment tool specifically for HDS (HDS-CAT), which needs further investigation and validation.[30]

HERBAL PRODUCTS THAT HAVE BEEN LINKED TO HEPATOTOXICITY

Ayurvedic herbal products

Ayurvedic medicine is the science of a plant-based system of healing applicable to a spectrum of disorders that originated is ancient India. It generally consists of numerous plants, but metals may also be present due to the practice of 'Rasa shastra' (combining herbs with metals, minerals and gems).[31] Notably, 20–22% of both US- and Indian-manufactured Ayurvedic medicines randomly purchased via the Internet in 2005 contain detectable lead, mercury or arsenic.[31] Although cases of heavy metal poisoning associated with Ayurvedic medicine have been continuously reported, this form of treatment is still utilised by the majority in rural India (1.1 billion people) and worldwide by the South Asian diaspora and others.[31, 32] Interestingly, despite being widely used, hepatotoxicity from Ayurvedic medicine has been rarely reported in the literature. Severe hepatitis has been documented in a woman who had treated herself for 9 months with various Indian Ayurvedic herbal products for her vitiligo, in which the key implicated ingredient was believed to be *Psoralea corylifolia*.[33] *Centella asiatica* (Gotu kola, Mandukaparni, Kannada), an ayurvedic medicine used mainly for leprosy, has been reported to be associated with granulomatous hepatitis and cirrhosis.[34, 35] Additionally, in the European RCT of Ayurvedic herbal combination, Liv.52 which contains capers, wild chicory, arjuna, black nightshade, yarrow, and others, for the treatment of alcoholic cirrhosis (N = 188), no effect on survival was seen in Child class A/B patients, but substantially increased liver-related mortality was observed in those with Child class C (2-year survival: 40% vs. 81% in those who adhered to treatment, P = 0.02), suggesting a potential detrimental effect of this Ayurvedic preparation.[36]

Atractylis gummifera and Callilepsis laureola (Impila)

Atractylis gummifera is a thistle located in the Mediterranean regions, where more than 26 species have been identified. These plants secrete a whitish glue-like substance often used by children as chewing gum, and also used as an antipyretic, antiemetic, abortifacient and a diuretic.[5] Ingestion of *A. gummifera* continues despite its well-known toxicity attributed to atractyloside and carboxyatractyloside, which are concentrated in the root of the plant.[5, 37] These two diterpenoid glucosides are capable of inhibiting mitochondrial oxidative phosphorylation by interaction with a mitochondrial protein, the adenine nucleotide translocator.[37] More than hundred cases of liver and renal injury associated with *A. gummifera* ingestion have been reported, and they frequently involved children.[38, 39] In addition, toxicity is reported with the cutaneous application.[40] The onset of toxicity usually begins within few hours after ingestion, and is characterised by headache, anxiety, vomiting, abdominal pain, diarrhoea, and convulsion, which then often leads to acute liver and renal failure, neurovegetative state and death.[38–41] There is no specific pharmacological treatment for *A. gummifera* intoxication available and all the current therapeutic approaches are only symptomatic, with LT being an option. *In vitro* experiments noted that some compounds such as verapamil, or dithiothreitol could protect against the toxic effects of atractyloside by blocking ADP-ATP conversion through inhibition of P450 cytochrome, but only if administered before atractyloside exposure.[37, 41] New therapeutic approaches could come from immunotherapy research; efforts to develop polyclonal antibodies against the toxic components of *A. gummifera* are in progress.[37, 41]

Callilepsis laureola (Impila), is a plant indigenous to the Natal region of South Africa, and has been used as a traditional remedy, mainly by the Zulu Tribe. Similar to *A. gummifera, C. laureola* also contains the toxic atractyloside.[42] Several cases of acute liver and renal failure have been reported with a mortality rate greater than 90% by 5 days.[43, 44] Interestingly, *C. laureola*-induced cytotoxicity in Hep G2 cells involves depletion of cellular glutathione and preventing glutathione depletion by

supplementing cells with N-acetylcysteine to reduce its cytotoxicity potential has been demonstrated.[45]

Chaparral

Chaparral (*Larrea tridentate*) is made from the leaves of a desert shrub, known as the creosote bush or greasewood, found in Southwestern United States and Mexico.[5] It has been used for the treatment of various conditions, such as pain, bronchitis, skin conditions, cancer, and also as an alternative medicine for AIDS.[52, 53] Currently, chaparral comes in the form of a tea, and as capsules, tablets and salves.[5, 53] It is perceived to have antimicrobial and antioxidant activities and its active ingredient is nordihydroguiaretic acid, a potent inhibitor of lipoxygenase and cyclooxygenase pathways.[5, 19]

Several reports on hepatotoxicity associated with ingestion of chaparral leaf, including acute and subacute hepatocellular injury, and cholestatic hepatitis, have been published.[54–57] Sheikh *et al.* reviewed 13 cases of chaparral-induced hepatotoxicity in 1997.[53] Most patients presented with jaundice with a marked increase in ALT within 3–52 weeks after ingestion, which often resolved 1–17 weeks after discontinuing the product. However, 2 patients developed ALF requiring LT, and 4 patients eventually evolved onto cirrhosis.[53] Histological findings ranged from biliary changes and cholestasis to massive hepatic necrosis, particularly in zone 3.[19, 53–57]

Chinese herbal medicines

Numerous herbs from China have been used for centuries as traditional medicine. Chinese herbal medicines, while being quite popular in the East, have also become highly popular among Western countries as a form of 'natural' alternative medicine; they are perceived to be free of side effects. Most traditional Chinese medicines are blends of 4–6 different herbs, but there is typically a primary pharmacologically active component referred to as the 'King herb'. The remaining constituents are believed to function as modifiers of toxicity, act synergistically with the King herb, improve the immune function or strengthen certain aspects of actions, and such conglomeration of constituents makes the identification and assignment of causative hepatotoxic compounds extremely difficult.[6] In addition, adulteration by synthetic drugs and heavy metals has also been reported.[58–60]

Jin Bu Huan *(Lypocodium serratum)* has been widely used as a sedative and analgesic, as it contains levo-tetrahydropalmatine, a potent neuroactive substance. In North America, it was marketed as 'anodyne tablets' in the 1990s, and subsequently was banned due to convincing reports of toxicity (i.e. central nervous system and respiratory depression, cardiovascular collapse, and hepatotoxicity) after both acute and chronic use.[61–64] In a series of 7 cases of Jin Bu Huan-associated liver injury, acute hepatitis occurred after 7–52 weeks (mean 20 weeks) of ingestion and usually resolved within 2–30 weeks (mean 8 weeks).[64] Liver biopsy specimens noted mild hepatitis, moderate fibrosis and micro vesicular steatosis, with or without eosinophilic infiltrates.[64] In addition, chronic hepatitis with bridging fibrosis has also been described.[63] The mechanism of hepatotoxicity is unclear, but an immune-mediating process might play a role based on the development of fever, rash and eosinophilia in many individuals.[5, 64]

Ma huang (*Ephedra sinica*) is used as a nasal decongestant and bronchodilator, as well as to aid weight loss. In a meta-analysis, it was noted to promote modest short-term weight loss (not sufficient data regarding long-term weight loss and the contribution from athletic performance), but was associated with increased rate of psychiatric and autonomic system issues, gastrointestinal symptoms and heart palpitations.[65] Liver injury, including severe hepatitis, ALF, and as fulminant exacerbation of AIH, has been described in association with ma huang ingestion,[66, 67] as well as with the use of multiple different commercial weight-loss herbal products containing ma huang.[68, 69]

Dai-saiko-to (Sho-saiko-to, TJ-19, Da-chai-hu-tang, Xiao-chai-hu-tang) is a Chinese herbal medicine that has been used widely in Japan for the treatment of liver diseases and is part of the Japanese Kampo medical system.[5, 38] Dai-saiko-to differs from Sho-saiko-to only in the proportion of herbal constituents and which contains bupleuri, pinelliae, scutellaria, ginseng, ginger, glycyrrhiza and jujube fruits.[5, 38] Several *in vitro* and *in vivo* studies suggested that this product may be effective in preventing hepatic inflammation, fibrosis and hepatocellular carcinoma.[3] There have been, however, reports of liver injury attributed to these products.[70–72] Itoh *et al.* reported 4 cases of acute hepatitis following a latency period of 1.5–3 months after ingestion of Sho-saiko-to, which improved with cessation and recurred with rechallenge.[71] The liver histology revealed centrilobular confluent necrosis or spotty necrosis, micro vesicular fatty change, acidophilic degeneration, and a granuloma.[71] Kamiyama *et al.* reported a case of AIH, which possibly was triggered by Dai-saiko-to and this was based on the development of fatigue, fever, ALT elevation,, and ANA titre of 1:2560 after 2 weeks of treatment. Alanine aminotransferase returned to normal after treatment with prednisolone.[72]

Geniposide is one of the major iridoid glycosides in Gardenia fruit (*Gardenia jasminoides*) and is used in several Chinese and Kampo herbal medicines (i.e. Shui-Zhi-Zi, Sansisi) to treat various conditions, such as febrile conditions, liver diseases and cancers. In rat livers, acute hepatotoxicity of geniposide at high doses was predictable and likely to be linked to oxidative stress.[73] Interestingly, a case series and review of case reports from Japan suggested that long-term use of geniposide-containing herbal medicines appears to be associated with mesenteric phlebosclerosis.[74] The mechanism is not well understood, but possibly is due to biotransformation of geniposide by intestinal microflora into more toxic metabolite, genipin, that is cytotoxic and can induce cross-link formation in collagen.[74]

Sporadic cases of liver toxicity attributed to other Chinese herbs containing *Paeonia* spp. *(*commonly used for eczema)[6, 75] and *Polygonum multiflorum* (Shou-wu-pian)[76–78] have also been described.

Germander

The blossoms of Germander (*Teucrium chamaedrys*), a plant found in Europe and the Middle East, have been used for thousands of years for a variety of conditions, such as dyspepsia, hypertension, gout, diabetes and obesity.[5, 6] It is available as tea, capsules and as an addition to liquor.[6] Many reports (mostly from France) of liver injury have been documented, and these include presentations as acute, chronic hepatitis and as ALF.[79–83] Most cases of hepatotoxicity occurred after 2 months of intake at the manufacturer's recommended doses (600–1600 mg/day).[79–83] Symptoms were nonspecific (anorexia, nausea, abdominal pain and jaundice) and were accompanied by a marked elevation of ALT. After withdrawal, jaundice generally disappeared within 8 weeks; however, the development of cirrhosis and relapse following accidental exposure have also been anecdotally reported.[80] Germander contains saponins, glycosides, flavonoids and furan-containing diterpenoids. Furan-containing diterpenoids are well-known to be cytotoxic and carcinogenic.[84–86] In rat studies, these constituents are oxidised by cytochrome P450 3A4 to reactive metabolites that bind to proteins, deplete cellular glutathione and protein thiols, and ultimately induce membrane disruption and hepatocyte apoptosis.[84–86]

Apart from the instances of hepatitis from *T. chamaedrys,* there have been anecdotal case reports involving other herbs in the same genus (*Teucrium*), including *T. polium*,[87–89] *T. capitatum*[90] and *T. viscidum*.[91] These herbal products are often used as hypoglycaemic agents to aid in treatment of diabetes. Notably, acute severe cholestasis, cholestatic hepatitis and ALF requiring LT can be associated with *T. polium* ingestion.[87, 92–94] Based on chemical analysis, hepatotoxic neo-clerodane diterpenoids have also been isolated from other species of *Teucrium*, including *T.alpestre, T. cuneifolium, T. divarication subsp. villosum* and *T. flavum subsp. hellenicum*.[95]

Greater celandine

Greater celandine (*Chelidonium majus*) is a plant found mainly in Europe and contains at least 20 different alkaloids, such as berberine, coptisine, chelerythrine and chelidonine. Its extracts have been used for the treatment of biliary disorders and irritable bowel syndrome.[5, 6] Several reports, mostly from Germany, where commercial drug preparations containing Greater celandine are widely available, described liver injury associated with this herb.[96–99] In the largest case series of 10 patients, all were women presenting with moderate elevation of ALT and ALP, which began often around 3 months after ingestion.[96] Marked cholestasis was observed in 5 patients, but liver failure did not occur. Most of the liver biopsies showed portal inflammation and eosinophilic infiltrates, and in all patients, discontinuation of greater celandine treatment led to normalisation of hepatic biochemical tests in 2–6 months. Interestingly, low titre of antinuclear and smooth muscle autoantibodies were noted in 8 cases, which may indicate low-grade autoimmunity.[96] Additional 40 cases of hepatic injury from *C. majus* have been reported to the German regulatory authorities. Based on these data, *C. majus* has been banned from oral use in Germany and other European countries, while the Australian Complementary Medicines Evaluation Committee has recently recommended that all oral products containing *C. majus* have a warning label and be used under professional healthcare supervision.[100]

Green tea (*Camellia sinensis*)

Green tea is very popular worldwide and is also a frequent ingredient in various dietary supplements used predominantly for weight loss.[2] Several reports of hepatotoxicity, including ALF, following the ingestion of numerous and different green tea preparations have been published since 1999.[101–106] A review of 34 published case reports and 2 unpublished cases suggests a causal association between green tea and liver damage. Majority of cases were judged as 'possible' according to the CIOMS score and a positive rechallenge occurred in 7 cases.[106] Patterns of liver injury were hepatocellular in

most cases, but cholestasis and a mixed pattern were also observed. Liver histology examination revealed inflammatory reactions, cholestasis, occasional steatosis and necrosis.[106–108] In addition, a case with features mimicking AIH (elevation of ALT, hyperglobulinemia, transient presence of antismooth-muscle antibodies and necroinflammation with interface hepatitis on liver histology) following green tea infusion has also been described.[109] The mechanism of hepatotoxicity is incompletely understood, but components responsible are probably catechins and their gallic acid esters, particularly epigallocatechin-3-gallate, which, under certain conditions such as fasting, can induce reactive oxygen species formation, and affect mitochondrial membrane potential. Although there is reason to be concerned regarding green tea-induced liver injury, a systematic review of 34 such cases (27 were categorised as possible causality and 7 as probable causality) performed by the US Pharmacopoeia has not uncovered a major safety issue and therefore a warning on the label of the product has not been implemented.[104]

While there is concern of hepatotoxicity, significant amount of data from both experimental and clinical studies have suggested the role of green tea in hepatoprotection and cancer prevention, as well as in 'optimizing' general health.[107, 108, 110, 111] Although heterogeneity among studies exists, a systematic review of 10 studies, including 4 RCTs, showed a significant protective role of green tea against various liver diseases.[110] Whether the potential risk of hepatotoxicity from green tea outweighs their benefits remains unclear.

Herbalife products

Herbalife products (Los Angeles, CA, USA) are distributed as herbal and dietary supplements in the form of drinks, tablets, capsules and energy bars for weight control, cosmetics, nutritional support and improvement in well-being, via online marketing and through independent sale agents. It is one of the largest weight management and nutritional supplement companies in the World, with activity in almost 60 countries, and sales of over 3 billion US dollars.[108] Since 2007, there have been several published reports of Herbalife hepatotoxicity from different countries (i.e. Argentina, Iceland, Israel, Spain and Switzerland) describing more than 34 cases.[108, 112–116] Pattern of liver injury was hepatocellular in the majority of cases, but mixed and cholestatic patterns were also observed. Severity ranged from mild-to-severe liver damage and included cases that developed cirrhosis and ALF requiring LT.[108, 115, 116] Causality relationship was assessed by various widely used scores, and it was considered 'probable' in most cases, although 'certain' (with positive rechallenge) cases were also reported.[108, 113, 115] The exact mechanism of liver injury has not been established, but Elinav *et al.* hypothesised that immune-mediated injury could be a possible explanation, based on their observation of plasma cell infiltrates and occasional transient presence of autoantibodies in some cases.[113] More recently, Stickel *et al.* reported on 2 cases of severe hepatotoxicity associated with consumption of Herbalife products contaminated with *Bacillus subtilis*. Causality according to CIOMS was scored as 'probable' in both cases, and histology showed cholestatic and lobular/portal hepatitis with cirrhosis in one patient, and biliary fibrosis with ductopenia in the other. The authors further demonstrated that culture supernatants of the *Bacillus subtilis* isolated from the products induced dose-dependent leakage of LDH from HepaG2 cells, which they interpreted as the basis for the liver injury, thus raising concern for the possibility of adulteration of Herbalife products with hepatotoxin-producing bacterial strains. Therefore, it seems quite likely that hepatotoxicity does occur among some people who receive these products, but the precise mechanism or the responsible agent in the products is uncertain, in part because, to date, the complete listing of the ingredients of these products is not known and the manufacturer apparently is unwilling to provide the needed information.[117] Besides, Herbalife representatives have so far challenged the causal relationship between consumption of their products and DILI, as well as confirming good quality control for ingredients and contaminants in their production lines.[118, 119]

Hydroxycut

Hydroxycut is a popular dietary supplement consisting of a variety of herbal mixtures that claim to enhance the ability to lose weight. Several cases of hepatotoxicity associated with Hydroxycut have been reported.[120–122] Most patients exhibited a hepatocellular pattern of injury with marked elevation of ALT, but some patients had a more insidious and usually cholestatic course.[120–122] Notably, cases of AIH-like features and ALF requiring liver transplantation have also been described.[120, 121] The responsible toxic ingredient is not entirely certain, but may be the consequence of *Camellia sinensis* present in the product.[121] In May 2009, the FDA issued a warning to stop using Hydroxycut products, which was followed by a voluntary recall of all its products by the manufacturer.[108, 121] Subsequently, a new formulation of Hydroxycut has been developed and is being sold.[108]

Kava

Kava (*Piper methysticum*) is a plant indigenous to the South Pacific Islands, including Hawaii, Vanuatu, Polynesia, Melanesia and some parts of Micronesia, where an extract from its rhizome is commonly used to prepare a traditional beverage for social and recreational purposes.[123, 124] In Western countries, dietary supplements containing kava are promoted as an agent to relieve stress, anxiety, and tension, as well as for sleeplessness and menopausal symptoms.[123, 124] Its efficacy for the treatment of anxiety is supported by a Cochrane meta-analysis.[125] Numerous reports of severe hepatotoxicity have been described in the US and Europe, and some of which have been confirmed by structured, quantitative and liver-specific causality assessment methods.[5, 6, 29, 38, 126–128] In an analysis of 36 cases of kava hepatotoxicity, the pattern of injury was both hepatocellular and cholestasis; majority of the patients were women, the cumulative dose and latency were highly variable, and ALF developed in 9 patients and 8 of whom underwent LT.[126] The US-FDA began advising consumers on the potential risk of severe liver injury associated with the use of kava-containing dietary supplements in the year 2002 and the products have been banned from the markets of some countries in Europe, although they are still available in the US, Canada, Australia, New Zealand and South Pacific Islands, as well as via the Internet.[124]

The mechanism of hepatotoxicity has not been clearly elucidated; however, several potential hepatotoxic constituents (i.e. pipermethystine, flavokavain B and mould hepatotoxins) and co-factors (i.e. alterations in hepatic microsomal cytochrome P450, cyclooxygenase inhibition, P-glycoprotein and glutathione) have been extensively reviewed by Teschke.[123, 129] The author suggested that kava hepatotoxicity is partly preventable by quality control, prescription adherence and avoidance of co-medications, since it occurs primarily due to daily overdose (exceeding 250 mg of kava lactones), prolonged treatment and the use of the kava plant's aerial parts, which may contain the hepatotoxic alkaloid pipermethysticin, and contaminated kava raw material.[123, 124, 129]

Pennyroyal

Pennyroyal (squawmint oil) is an herb containing pulegone and a smaller amount of other monoterpenes, which often is in a form of oil.[5, 19] It has long been used as an abortifacient despite its potentially lethal hepatotoxic and neurotoxic effects.[130] Pennyroyal's toxicity is believed to be mainly from menthofuran, a metabolite of pulegone, which is oxidised by cytochrome P450. In addition, pulegone markedly depletes glutathione as measured in both liver tissue and plasma.[131] Therefore, drugs inhibiting cytochrome P450 (i.e. cimetidine and disulfuram) and/or replacement of glutathione with N-acetylcysteine may theoretically alleviate or prevent pennyroyal hepatotoxicity.[19, 131, 132] Anderson *et al.* published a report with a literature review of 22 cases of hepatotoxicity associated with pennyroyal oil.[130] Patients often developed severe gastrointestinal upset and central nervous system effects within 1–2 h following ingestion of the oil. Severe/fatal hepatic necrosis and multiorgan failure seemed to occur when more than 15 mL was ingested.[130] One patient was successfully treated by N-acetylcysteine.[130]

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PA) are found in more than 350 plant species worldwide. These alkaloids have been well-recognised in causing hepatotoxicity for over 70 years, particularly with *Senecio, Heliotropium, Crotalaria,* and *Symphytium* (Comfrey) species.[19, 133–137] The key pattern of liver injury is VOD, newly termed sinusoidal obstruction syndrome (SOS), which was first reported in Jamaican children who drank bush tea for their illness.[133] Subsequently, several cases of VOD associated with an ingestion of PA-containing plants (most often as herbal tea) have been reported mainly from the Southern US, Africa, and Asia, as well as sporadically from Western Countries.[19, 134–138]

PA-associated VOD typically presents with ascites, oedema and hepatomegaly. The clinical onset and severity are variable. In the acute form, abdominal pain develops suddenly, often with jaundice and markedly elevated ALT levels, and with rapid deterioration ending in death.[19, 133–138] The pathogenic process begins with damage to sinusoid endothelial cells that leads to partial obstruction of the sinusoidal lumens, thereby causing obstruction to the sinusoidal blood flow.[38] Liver histology is characterised by nonthrombotic occlusion of small terminal hepatic venules, leading to sinusoidal dilatation and, eventually, haemorrhagical centrilobular necrosis.[19, 133–138] Acute VOD is fatal in 15–20% of patients, with it being worse in adults as compared with children.[133] Complete recovery has been observed in about half of the patients, whereas approximately 15% of patients may have a protracted course of liver injury, characterised by perivenular and bridging fibrosis, and some may die from decompensated liver disease several years later.[19, 133–138] A smaller proportion of patients may have subacute or chronic onset of illness, which may insidiously progress to cirrhosis and portal hypertension.[19] In animal models,

the hepatotoxicity of PA seems to be related to the biotransformation by cytochrome P450 3A4 into unstable toxic metabolites (pyrrole derivatives) that may act as alkylating agents and this depends on the type and total dose of PA ingested, along with susceptibility to the alkaloids.[139–141] Notably, herb–drug or herb–herb interactions involving cytochrome P450 are likely to affect PA-associated VOD susceptibility and severity, as toxicity can be amplified by concomitant use of phenobarbital via the induction of cytochrome P450.[6, 141] Acute VOD may result from a short time exposure to high doses, whereas chronic liver injury may be caused by prolonged exposure to even small doses of PA.[139–141]

The management of PA-associated VOD is mainly supportive. Defibrotide, a polydisperse oligonucleotide with local antithrombotic, anti-ischaemic and anti-inflammatory activity, appears to be effective for severe VOD following haematopoietic stem cell transplant;[142] however, its role in the treatment of PA-associated VOD is unknown. As soon as acute or chronic liver failure appears imminent, LT may be the only effective therapy.[6]

Other herbal and dietary supplements

Numerous other herbal products, including camphor oil (*Cinnamomum camphora,* Vicks VapoRub),[38, 143] black cohosh,[46–51] saw palmetto (*Serrenoa repens*),[144]Noni juice (*Morinda citrifolia*),[145–148] Cascara (*Cascara sagrada*),[38, 149] mistletoe (*Viscus album*),[150–152] skullcap (*Scutellaria*),[153, 154] valerian (*Valeriana officinalis*),[155] senna (*Cassia angustifolia* and *C. acutifolia*),[156–158] usnic acid,[159–161] Margosa oil (*Antelaea azadirachta, Azadirachta indica*)[6, 38] and Aloe vera,[162, 163] as well as dietary supplements, including vitamin A have been described to cause hepatotoxicity.[108, 164–166] Furthermore, preparations containing anabolic steroids[108, 167, 168] have also been linked to liver injury and are summarised in Table S1.

HERB–DRUG INTERACTIONS

In addition to the potential for direct hepatotoxicity, some of these herbs may have interactions with certain prescription medications by various mechanisms leading to adverse events, including potentiation of risk for hepatotoxicity, renal toxicity, abnormal bleeding, graft rejection and cardiovascular collapse.[169–171] Many herbs have been identified as substrates, inhibitors, and/or inducers of various cytochrome P450 enzymes, such as St. John's wort, garlic, pepper, licorice, flavonoids, triterpenoids and anthraquinones.[172] For example, St. John's wort is a potent inducer of CYP3A4, mediated by activation of the

Table 2 | Herb–drug interactions relevant to hepatology [Adapted from Ref. (38)]

Medications	Herbs	Interactions and potential consequences
Warfarin and aspirin	Danshen (*S. miltiorrhiza*)	Increased INR → bleeding risk
	Dong quai (*A. sinensis*)	Increased INR → bleeding risk
	Garlic	Increased INR → bleeding risk
	Papaya	Increased INR → bleeding risk
	Tamarind	Increased aspirin level → bleeding risk
	Feverfew	Platelet dysfunction → bleeding risk
	Gingko biloba	Platelet dysfunction → bleeding risk
	Ginseng	Decreased INR → clotting risk
	St. John's wort	Decreased INR → clotting risk
	Devil's claw (*H. cumbens*)	Purpura
CYP34A drugs	Pyrrolizidines	CYP3A4 induction → hepatotoxicity
	Germander	CYP3A4 induction → hepatotoxicity
Cyclosporine	St. John's wort	CYP3A4 induction → rejection risk
	Grape fruit juice	CYP3A4 induction → rejection risk
Methotrexate	St. John's wort	Increased methotrexate level and toxicity
	Echinacea	Increased hepatotoxicity ?
Prednisolone	Ginseng	Possible additive effect
	Glycyrrhizin (licorice root)	Reduced clearance → hypokalemia
	Sho-saiko-to	Altered clearance → low prednisolone level
Protease inhibitors	St. John's wort	CYP3A4 induction → suboptimal antiviral activity
	Garlic	CYP3A4 induction → suboptimal antiviral activity
Spironolactone	Glycyrrhizin (licorice root)	Mineralocorticoid → low spironolactone level
Benzodiazepines	Kava	Increased sedative effects

CYP, cytochrome P450; INR, international ratio.

pregnane X receptor, which can then potentiate the intrinsic hepatotoxicity of other substances, such as germander and acetaminophen, by way of an increased conversion to toxic metabolites.[19, 172] It also enhances plasma clearance of a number of drugs, such as cyclosporine and protease inhibitors, which can complicate the management of posttransplant immunosuppression, as well as HIV and hepatitis C therapy.[169, 170, 172, 173] In addition, coadministration of St. John's wort significantly increased the systemic exposure and toxicity of methotrexate in a rat model.[174] Several herbs, including Danshen, Dong quai, garlic, papaya, tamarind, feverfew, and Gingko biloba, have been associated with an increased risk of bleeding in patients who are on warfarin and/or aspirin. Other herb–drug interactions that may result in hepatotoxicity or significantly affect practice are summarised in Table 2.

CONCLUSION

As herbal products continue to be used widely around the World, herbal hepatotoxicity will continue to be observed. Such events are not necessarily unique to herbal medications as they can be seen with prescription medications such as antibiotics, anticonvulsants, etc. It is therefore imperative that the recognition and reporting of herbal hepatotoxicity be held to the same standards as prescription medications. Liver injury is mostly hepatocellular, but mixed and cholestatic patterns can also occur, and the severity ranges from mild injury to ALF, as well as with evolution to chronicity. The diagnosis of herbal hepatotoxicity depends on a proper knowledge of the available literature on hepatotoxicity with the spectrum of herbal preparations ingested and also on a heightened awareness for such hepatotoxic events. Advances in the understanding of the frequency, the pathogenesis, the clinical manifestations and outcomes are needed to be able to improve herbal medicine safety.

AUTHORSHIP

Guarantor of the article: K. R. Reddy.

Author contributions: C. Bunchorntavakul conceptualized, searched and reviewed the literature, and drafted the manuscript. K. R. Reddy conceptualized and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Herbal and dietary products associated with liver injury: application, toxic mechanism and clinical features.

REFERENCES

1. Schuppan D, Jia JD, Brinkhaus B, Hahn EG. Herbal products for liver diseases: a therapeutic challenge for the new millennium. *Hepatology* 1999; **30**: 1099–104.
2. Navarro VJ. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis* 2009; **29**: 373–82.
3. Verma S, Thuluvath PJ. Complementary and alternative medicine in hepatology: review of the evidence of efficacy. *Clin Gastroenterol Hepatol* 2007; **5**: 408–16.
4. Bent S, Ko R. Commonly used herbal medicines in the United States: a review. *Am J Med* 2004; **116**: 478–85.
5. Seeff LB. Herbal hepatotoxicity. *Clin Liver Dis* 2007; **11**: 577–96.
6. Stickel F, Patsenker E, Schuppan D. Herbal hepatotoxicity. *J Hepatol* 2005; **43**: 901–10.
7. Andrade RJ, Lucena MI, Fernandez MC, *et al.* Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005; **129**: 512–21.
8. Chalasani N, Fontana RJ, Bonkovsky HL, *et al.* Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; **135**: 1924–34, 1934 e1-4.
9. Ibanez L, Perez E, Vidal X, Laporte JR. Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. *J Hepatol* 2002; **37**: 592–600.
10. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; **52**: 2065–76.
11. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 2004; **10**: 1018–23.
12. 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.
13. Suk KT, Kim DJ, Kim CH, *et al.* A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol* 2012; **107**: 1380–7.
14. 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.

15. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. *Am J Gastroenterol* 2010; **105**: 2396–404.
16. Melchart D, Linde K, Weidenhammer W, Hager S, Shaw D, Bauer R. Liver enzyme elevations in patients treated with traditional Chinese medicine. *JAMA* 1999; **282**: 28–9.
17. Yun YJ, Nah SS, Park JH, *et al.* Assessment of prescribed herbal medicine on liver function in Korea: a prospective observational study. *J Altern Complement Med* 2008; **14**: 1131–6.
18. Sangsuwan C, Udompanthurak S, Vannasaeng S, Thamlikitkul V. Randomized controlled trial of Tinospora crispa for additional therapy in patients with type 2 diabetes mellitus. *J Med Assoc Thai* 2004; **87**: 543–6.
19. Schiano TD. Hepatotoxicity and complementary and alternative medicines. *Clin Liver Dis* 2003; **7**: 453–73.
20. Agarwal VK, McHutchison JG, Hoofnagle JH. Important elements for the diagnosis of drug-induced liver injury. *Clin Gastroenterol Hepatol* 2010; **8**: 463–70.
21. Dalton HR, Fellows HJ, Stableforth W, *et al.* The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther* 2007; **26**: 1429–35.
22. Davern TJ, Chalasani N, Fontana RJ, *et al.* Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology* 2011; **141**: 1665–72 e1-9.
23. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990; **11**: 272–6.
24. Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997; **26**: 664–9.
25. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs–II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol* 1993; **46**: 1331–6.
26. Rochon J, Protiva P, Seeff LB, *et al.* Reliability of the Roussel Uclaf Causality Assessment Method for assessing causality in drug-induced liver injury. *Hepatology* 2008; **48**: 1175–83.
27. Shapiro MA, Lewis JH. Causality assessment of drug-induced hepatotoxicity: promises and pitfalls. *Clin Liver Dis* 2007; **11**: 477–505, v.
28. Nin Chau T, Cheung WI, Ngan T, *et al.* Causality assessment of herb-induced liver injury using multidisciplinary approach and Roussel Uclaf Causality Assessment Method (RUCAM). *Clin Toxicol (Phila)* 2011; **49**: 34–9.
29. Teschke R. Hepatotoxicity by drugs and dietary supplements: safety perspectives on clinical and regulatory issues. *Ann Hepatol* 2009; **8**: 184–95.
30. Navaro VJ, Barnhart HX, Bonkovsky HL, *et al.* Diagnosing hepatotoxicity attributable to herbal and dietary supplements: test-retest reliability of novel causality assessment tool. *J Hepatol* 2012; **55**(Suppl. 2): S536.
31. Saper RB, Phillips RS, Sehgal A, *et al.* Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. *JAMA* 2008; **300**: 915–23.
32. Gogtay NJ, Bhatt HA, Dalvi SS, Kshirsagar NA. The use and safety of non-allopathic Indian medicines. *Drug Saf* 2002; **25**: 1005–19.
33. Teschke R, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: a structured causality assessment. *Ann Hepatol* 2009; **8**: 258–66.
34. Dantuluri S, North-Lewis P, Karthik SV. Gotu Kola induced hepatotoxicity in a child - need for caution with alternative remedies. *Dig Liver Dis* 2011; **43**: 500.
35. Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of *Centella asiatica*. *Rev Esp Enferm Dig* 2005; **97**: 115–24.
36. Fleig WW, Morgan MY, Holzer MA. European multicenter study group. The ayurvedic drug Liv.52 in patients with alcoholic cirrhosis. Results of a prospective, randomized, double-blind, placebo-controlled clinical trial. *J Hepatol* 1997; **126**(Suppl. 1): 127.
37. Daniele C, Dahamna S, Firuzi O, Sekfali N, Saso L, Mazzanti G. *Atractylis gummifera* L. poisoning: an ethnopharmacological review. *J Ethnopharmacol* 2005; **97**: 175–81.
38. Strader DB, Navarro VJ, Seeff LB. Hepatotoxicity of herbal preparations. In: Boyer TD, Manns MP, Sanyal AJ, eds. *Zakim and Boyer's Hepatology: A Textbook of Liver Disease*, 6th edn. Philadelphia, PA: Saunders, 2012; 462–75.
39. Ahid S, Ait El Cadi M, Meddah B, Cherrah Y. *Atractylis gummifera*: from poisoning to the analytic methods. *Ann Biol Clin (Paris)* 2012; **70**: 263–8.
40. Bouziri A, Hamdi A, Menif K, Ben Jaballah N. Hepatorenal injury induced by cutaneous application of *Atractylis gummifera* L. *Clin Toxicol (Phila)* 2010; **48**: 752–4.
41. Hamouda C, Hedhili A, Ben Salah N, Zhioua M, Amamou M. A review of acute poisoning from *Atractylis gummifera* L. *Vet Hum Toxicol* 2004; **46**: 144–6.
42. Steenkamp PA, Harding NM, van Heerden FR, van Wyk BE. Determination of atractyloside in *Callilepis laureola* using solid-phase extraction and liquid chromatography-atmospheric pressure ionisation mass spectrometry. *J Chromatogr A* 2004; **1058**: 153–62.
43. Popat A, Shear NH, Malkiewicz I, *et al.* The toxicity of *Callilepis laureola*, a South African traditional herbal medicine. *Clin Biochem* 2001; **34**: 229–36.
44. Stewart MJ, Steenkamp V, van der Merwe S, Zuckerman M, Crowther NJ. The cytotoxic effects of a traditional Zulu remedy, impila (*Callilepis laureola*). *Hum Exp Toxicol* 2002; **21**: 643–7.
45. Popat A, Shear NH, Malkiewicz I, Thomson S, Neuman MG. Mechanism of Impila (*Callilepis laureola*)-induced cytotoxicity in Hep G2 cells. *Clin Biochem* 2002; **35**: 57–64.
46. Teschke R, Schwarzenboeck A, Schmidt-Taenzer W, Wolff A, Hennermann KH. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. *Ann Hepatol* 2011; **10**: 249–59.
47. 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.
48. 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.
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. Mahady GB, Low Dog T, Barrett ML, *et al.* United States Pharmacopeia review of the black cohosh case reports of hepatotoxicity. *Menopause* 2008; **15**(4 Pt 1): 628–38.
51. Naser B, Schnitker J, Minkin MJ, de Arriba SG, Nolte KU, Osmers R. Suspected black cohosh hepatotoxicity: no evidence by meta-analysis of randomized controlled clinical trials for isopropanolic black cohosh extract. *Menopause* 2011; **18**: 366–75.
52. Kassler WJ, Blanc P, Greenblatt R. The use of medicinal herbs by human immunodeficiency virus-infected

patients. *Arch Intern Med* 1991; **151**: 2281–8.
53. Sheikh NM, Philen RM, Love LA. Chaparral-associated hepatotoxicity. *Arch Intern Med* 1997; **157**: 913–9.
54. Batchelor WB, Heathcote J, Wanless IR. Chaparral-induced hepatic injury. *Am J Gastroenterol* 1995; **90**: 831–3.
55. Gordon DW, Rosenthal G, Hart J, Sirota R, Baker AL. Chaparral ingestion. The broadening spectrum of liver injury caused by herbal medications. *JAMA* 1995; **273**: 489–90.
56. Katz M, Saibil F. Herbal hepatitis: subacute hepatic necrosis secondary to chaparral leaf. *J Clin Gastroenterol* 1990; **12**: 203–6.
57. Kauma H, Koskela R, Makisalo H, Autio-Harmainen H, Lehtola J, Hockerstedt K. Toxic acute hepatitis and hepatic fibrosis after consumption of chaparral tablets. *Scand J Gastroenterol* 2004; **39**: 1168–71.
58. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. *J Intern Med* 2002; **252**: 107–13.
59. Espinoza EO, Mann MJ, Bleasdell B. Arsenic and mercury in traditional Chinese herbal balls. *N Engl J Med* 1995; **333**: 803–4.
60. Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. *J Clin Pharmacol* 1997; **37**: 344–50.
61. Horowitz RS, Feldhaus K, Dart RC, Stermitz FR, Beck JJ. The clinical spectrum of Jin Bu Huan toxicity. *Arch Intern Med* 1996; **156**: 899–903.
62. McRae CA, Agarwal K, Mutimer D, Bassendine MF. Hepatitis associated with Chinese herbs. *Eur J Gastroenterol Hepatol* 2002; **14**: 559–62.
63. Picciotto A, Campo N, Brizzolara R, *et al.* Chronic hepatitis induced by Jin Bu Huan. *J Hepatol* 1998; **28**: 165–7.
64. Woolf GM, Petrovic LM, Rojter SE, *et al.* Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med* 1994; **121**: 729–35.
65. Shekelle PG, Hardy ML, Morton SC, *et al.* Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA* 2003; **289**: 1537–45.
66. Borum ML. Fulminant exacerbation of autoimmune hepatitis after the use of ma huang. *Am J Gastroenterol* 2001; **96**: 1654–5.
67. Skoulidis F, Alexander GJ, Davies SE. Ma huang associated acute liver failure requiring liver transplantation. *Eur J Gastroenterol Hepatol* 2005; **17**: 581–4.
68. Favreau JT, Ryu ML, Braunstein G, *et al.* Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med* 2002; **136**: 590–5.
69. 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.
70. 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.
71. Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine, syo-saiko-to (xiao-chai-hu-tang). *Dig Dis Sci* 1995; **40**: 1845–8.
72. Kamiyama T, Nouchi T, Kojima S, Murata N, Ikeda T, Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. *Am J Gastroenterol* 1997; **92**: 703–4.
73. Ding Y, Zhang T, Tao JS, Zhang LY, Shi JR, Ji G. Potential hepatotoxicity of geniposide, the major iridoid glycoside in dried ripe fruits of Gardenia jasminoides (Zhi-zi). *Nat Prod Res* 2012 [Epub ahead of print].
74. Hiramatsu K, Sakata H, Horita Y, *et al.* Mesenteric phlebosclerosis associated with long-term oral intake of geniposide, an ingredient of herbal medicine. *Aliment Pharmacol Ther* 2012; **36**: 575–86.
75. Galloway JH, Marsh ID, Bittiner SB, *et al.* Chinese herbs for eczema, the active compound? *Lancet* 1991; **337**: 566.
76. Furukawa M, Kasajima S, Nakamura Y, *et al.* Toxic hepatitis induced by show-wu-pian, a Chinese herbal preparation. *Intern Med* 2010; **49**: 1537–40.
77. 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.
78. 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**: 115–7.
79. Castot A, Larrey D. Hepatitis observed during a treatment with a drug or tea containing Wild Germander. Evaluation of 26 cases reported to the Regional Centers of Pharmacovigilance. *Gastroenterol Clin Biol* 1992; **16**: 916–22.
80. Larrey D, Vial T, Pauwels A, *et al.* Hepatitis after germander (*Teucrium chamaedrys*) administration: another instance of herbal medicine hepatotoxicity. *Ann Intern Med* 1992; **117**: 129–32.
81. Gori L, Galluzzi P, Mascherini V, *et al.* Two contemporary cases of hepatitis associated with *Teucrium chamaedrys* L. decoction use: case reports and review of literature. *Basic Clin Pharmacol Toxicol* 2011; **109**: 521–6.
82. Laliberte L, Villeneuve JP. Hepatitis after the use of germander, a herbal remedy. *CMAJ* 1996; **154**: 1689–92.
83. Mostefa-Kara N, Pauwels A, Pines E, Biour M, Levy VG. Fatal hepatitis after herbal tea. *Lancet* 1992; **340**: 674.
84. Lekehal M, Pessayre D, Lereau JM, Moulis C, Fouraste I, Fau D. Hepatotoxicity of the herbal medicine germander: metabolic activation of its furano diterpenoids by cytochrome P450 3A Depletes cytoskeleton-associated protein thiols and forms plasma membrane blebs in rat hepatocytes. *Hepatology* 1996; **24**: 212–8.
85. Loeper J, Descatoire V, Letteron P, *et al.* Hepatotoxicity of germander in mice. *Gastroenterology* 1994; **106**: 464–72.
86. 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.
87. Mattei A, Rucay P, Samuel D, Feray C, Reynes M, Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration. *J Hepatol* 1995; **22**: 597.
88. Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy *Teucrium polium* L. *Eur J Gastroenterol Hepatol* 2006; **18**: 681–3.
89. 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.
90. Dourakis SP, Papanikolaou IS, Tzemanakis EN, Hadziyannis SJ. Acute hepatitis associated with herb (Teucrium capitatum L.) administration. *Eur J Gastroenterol Hepatol* 2002; **14**: 693–5.
91. Poon WT, Chau TL, Lai CK, *et al.* Hepatitis induced by *Teucrium viscidum*. *Clin Toxicol (Phila)* 2008; **46**: 819–22.

92. Mazokopakis E, Lazaridou S, Tzardi M, Mixaki J, Diamantis I, Ganotakis E. Acute cholestatic hepatitis caused by *Teucrium polium* L. *Phytomedicine* 2004; **11**: 83–4.
93. 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.
94. Mimidis KP, Papadopoulos VP, Baltatzidis G, Giatromanolaki A, Sivridis E, Kartalis G. Severe acute cholestasis caused by *Teucrium polium*. *J Gastrointestin Liver Dis* 2009; **18**: 387–8.
95. Piozzi F, Bruno M, Ciriminna R, *et al.* Putative hepatotoxic neoclerodane diterpenoids from Teucrium species. *Planta Med* 1997; **63**: 483–4.
96. Benninger J, Schneider HT, Schuppan D, Kirchner T, Hahn EG. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Gastroenterology* 1999; **117**: 1234–7.
97. Hardeman E, Van Overbeke L, Ilegems S, Ferrante M. Acute hepatitis induced by greater celandine (*Chelidonium majus*). *Acta Gastroenterol Belg* 2008; **71**: 281–2.
98. Moro PA, Cassetti F, Giugliano G, *et al.* Hepatitis from Greater celandine (*Chelidonium majus* L.): review of literature and report of a new case. *J Ethnopharmacol* 2009; **124**: 328–32.
99. Stickel F, Poschl G, Seitz HK, Waldherr R, Hahn EG, Schuppan D. Acute hepatitis induced by Greater Celandine (*Chelidonium majus*). *Scand J Gastroenterol* 2003; **38**: 565–8.
100. Gilca M, Gaman L, Panait E, Stoian I, Atanasiu V. *Chelidonium majus*–an integrative review: traditional knowledge versus modern findings. *Forsch Komplementmed* 2010; **17**: 241–8.
101. 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.
102. Javaid A, Bonkovsky HL. Hepatotoxicity due to extracts of Chinese green tea (*Camellia sinensis*): a growing concern. *J Hepatol* 2006; **45**: 334–5; author reply 335-6.
103. Jimenez-Saenz M, Martinez-Sanchez Mdel C. Acute hepatitis associated with the use of green tea infusions. *J Hepatol* 2006; **44**: 616–7.
104. Sarma DN, Barrett ML, Chavez ML, *et al.* Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf* 2008; **31**: 469–84.
105. Verhelst X, Burvenich P, Van Sassenbroeck D, Gabriel C, Lootens M, Baert D. Acute hepatitis after treatment for hair loss with oral green tea extracts (*Camellia Sinensis*). *Acta Gastroenterol Belg* 2009; **72**: 262–4.
106. Mazzanti G, Menniti-Ippolito F, Moro PA, *et al.* Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009; **65**: 331–41.
107. 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.
108. Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. *Liver Int* 2011; **31**: 595–605.
109. Vanstraelen S, Rahier J, Geubel AP. Jaundice as a misadventure of a green tea (*Camellia sinensis*) lover: a case report. *Acta Gastroenterol Belg* 2008; **71**: 409–12.
110. Jin X, Zheng RH, Li YM. Green tea consumption and liver disease: a systematic review. *Liver Int* 2008; **28**: 990–6.
111. Mukhtar H, Ahmad N. Tea polyphenols: prevention of cancer and optimizing health. *Am J Clin Nutr* 2000; **71**(Suppl.): 1698S–702S.
112. Chao S, Anders M, Turbay M, Olaiz E, Mc Cormack L, Mastai R. Toxic hepatitis by consumption Herbalife products a case report. *Acta Gastroenterol Latinoam* 2008; **38**: 274–7.
113. Elinav E, Pinsker G, Safadi R, *et al.* Association between consumption of Herbalife nutritional supplements and acute hepatotoxicity. *J Hepatol* 2007; **47**: 514–20.
114. Manso G, Lopez-Rivas L, Salgueiro ME, *et al.* Continuous reporting of new cases in Spain supports the relationship between Herbalife(R) products and liver injury. *Pharmacoepidemiol Drug Saf* 2011; **20**: 1080–7.
115. 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.
116. Stickel F, Droz S, Patsenker E, Bogli-Stuber K, Aebi B, Leib SL. Severe hepatotoxicity following ingestion of Herbalife nutritional supplements contaminated with Bacillus subtilis. *J Hepatol* 2009; **50**: 111–7.
117. Seeff LB. Are herbals as safe as their advocates believe? *J Hepatol* 2009; **50**: 13–6.
118. Appelhans K, Smith C, Bejar E, Henig YS. Revisiting acute liver injury associated with herbalife products. *World J Hepatol* 2011; **3**: 275–7.
119. Ignarro L, Heber D, Henig YS, Bejar E. Herbalife nutritional products and liver injury revisited. *J Hepatol* 2008; **49**: 291–3.
120. Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. *World J Gastroenterol* 2008; **14**: 6999–7004.
121. Fong TL, Klontz KC, Canas-Coto A, *et al.* Hepatotoxicity due to hydroxycut: a case series. *Am J Gastroenterol* 2010; **105**: 1561–6.
122. Lobb A. Hepatoxicity associated with weight-loss supplements: a case for better post-marketing surveillance. *World J Gastroenterol* 2009; **15**: 1786–7.
123. Teschke R. Kava hepatotoxicity: pathogenetic aspects and prospective considerations. *Liver Int* 2010; **30**: 1270–9.
124. Teschke R, Schulze J. Risk of kava hepatotoxicity and the FDA consumer advisory. *JAMA* 2010; **304**: 2174–5.
125. Pittler MH, Edzard E. Kava extract for treating anxiety. *Cochrane Database Syst Rev* 2001; **4**: CD003383.
126. Stickel F, Baumuller HM, Seitz K, *et al.* Hepatitis induced by Kava (Piper methysticum rhizoma). *J Hepatol* 2003; **39**: 62–7.
127. Teschke R. Kava hepatotoxicity–a clinical review. *Ann Hepatol* 2010; **9**: 251–65.
128. Teschke R, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol* 2008; **20**: 1182–93.
129. Teschke R, Qiu SX, Lebot V. Herbal hepatotoxicity by kava: update on pipermethystine, flavokavain B, and mould hepatotoxins as primarily assumed culprits. *Dig Liver Dis* 2011; **43**: 676–81.
130. Anderson IB, Mullen WH, Meeker JE, *et al.* Pennyroyal toxicity: measurement of toxic metabolite levels in two cases and review of the literature. *Ann Intern Med* 1996; **124**: 726–34.
131. Thomassen D, Slattery JT, Nelson SD. Menthofuran-dependent and independent aspects of pulegone hepatotoxicity: roles of glutathione. *J Pharmacol Exp Ther* 1990; **253**: 567–72.
132. Sztajnkrycer MD, Otten EJ, Bond GR, Lindsell CJ, Goetz RJ. Mitigation of pennyroyal oil hepatotoxicity in the mouse. *Acad Emerg Med* 2003; **10**: 1024–8.
133. Bras G, Jelliffe DB, Stuart KL. Veno-occlusive disease of liver with nonportal type of cirrhosis, occurring

in Jamaica. *AMA Arch Pathol* 1954; **57**: 285–300.
134. Tandon RK, Tandon BN, Tandon HD, *et al.* Study of an epidemic of venoocclusive disease in India. *Gut* 1976; **17**: 849–55.
135. Mohabbat O, Younos MS, Merzad AA, Srivastava RN, Sediq GG, Aram GN. An outbreak of hepatic veno-occlusive disease in north-western Afghanistan. *Lancet* 1976; **2**: 269–71.
136. Stillman AS, Huxtable R, Consroe P, Kohnen P, Smith S. Hepatic veno-occlusive disease due to pyrrolizidine (Senecio) poisoning in Arizona. *Gastroenterology* 1977; **73**: 349–52.
137. Bach N, Thung SN, Schaffner F. Comfrey herb tea-induced hepatic veno-occlusive disease. *Am J Med* 1989; **87**: 97–9.
138. Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic venocclusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. *Gastroenterology* 1985; **88**: 1050–4.
139. DeLeve LD, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. *Hepatology* 1996; **23**: 589–99.
140. Huxtable RJ. New aspects of the toxicology and pharmacology of pyrrolizidine alkaloids. *Gen Pharmacol* 1979; **10**: 159–67.
141. Mattocks AR. Toxicity of pyrrolizidine alkaloids. *Nature* 1968; **217**: 723–8.
142. Richardson PG, Soiffer RJ, Antin JH, *et al.* Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant* 2010; **16**: 1005–17.
143. Jimenez JF, Brown AL, Arnold WC, Byrne WJ. Chronic camphor ingestion mimicking Reye's syndrome. *Gastroenterology* 1983; **84**: 394–8.
144. Singh YN, Devkota AK, Sneeden DC, Singh KK, Halaweish F. Hepatotoxicity potential of saw palmetto (*Serenoa repens*) in rats. *Phytomedicine* 2007; **14**: 204–8.
145. Stadlbauer V, Fickert P, Lackner C, *et al.* Hepatotoxicity of NONI juice: report of two cases. *World J Gastroenterol* 2005; **11**: 4758–60.
146. 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.
147. Yuce B, Gulberg V, Diebold J, Gerbes AL. Hepatitis induced by Noni juice from *Morinda citrifolia*: a rare cause of hepatotoxicity or the tip of the iceberg? *Digestion* 2006; **73**: 167–70.
148. Stadlbauer V, Weiss S, Payer F, Stauber RE. Herbal does not at all mean innocuous: the sixth case of hepatotoxicity associated with *Morinda citrifolia* (noni). *Am J Gastroenterol* 2008; **103**: 2406–7.
149. 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.
150. Harvey J, Colin-Jones DG. Mistletoe hepatitis. *Br Med J (Clin Res Ed)* 1981; **282**: 186–7.
151. Hullar TE, Sapers BL, Ridker PM, Jenkins RL, Huth TS, Farraye FA. Herbal toxicity and fatal hepatic failure. *Am J Med* 1999; **106**: 267–8.
152. MacGregor FB, Abernethy VE, Dahabra S, Cobden I, Hayes PC. Hepatotoxicity of herbal remedies. *BMJ* 1989; **299**: 1156–7.
153. Haouzi D, Lekehal M, Moreau A, *et al.* Cytochrome P450-generated reactive metabolites cause mitochondrial permeability transition, caspase activation, and apoptosis in rat hepatocytes. *Hepatology* 2000; **32**: 303–11.
154. Linnebur SA, Rapacchietta OC, Vejar M. Hepatotoxicity associated with chinese skullcap contained in Move Free Advanced dietary supplement: two case reports and review of the literature. *Pharmacotherapy* 2010; **30**: 750, 258e–62e.
155. Cohen DL, Del Toro Y. A case of valerian-associated hepatotoxicity. *J Clin Gastroenterol* 2008; **42**: 961–2.
156. Soyuncu S, Cete Y, Nokay AE. Portal vein thrombosis related to *Cassia angustifolia*. *Clin Toxicol (Phila)* 2008; **46**: 774–7.
157. Vanderperren B, Rizzo M, Angenot L, Haufroid V, Jadoul M, Hantson P. Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacother* 2005; **39**: 1353–7.
158. Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. *Lancet* 1991; **337**: 372–3.
159. 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.
160. Guo L, Shi Q, Fang JL, *et al.* Review of usnic acid and *Usnea barbata* toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2008; **26**: 317–38.
161. 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.
162. Rabe C, Musch A, Schirmacher P, Kruis W, Hoffmann R. Acute hepatitis induced by an Aloe vera preparation: a case report. *World J Gastroenterol* 2005; **11**: 303–4.
163. Yang HN, Kim DJ, Kim YM, *et al.* Aloe-induced toxic hepatitis. *J Korean Med Sci* 2010; **25**: 492–5.
164. Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. *Gastroenterology* 1991; **100**: 1701–9.
165. Nollevaux MC, Guiot Y, Horsmans Y, *et al.* Hypervitaminosis A-induced liver fibrosis: stellate cell activation and daily dose consumption. *Liver Int* 2006; **26**: 182–6.
166. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr* 2006; **83**: 191–201.
167. Kafrouni MI, Anders RA, Verma S. Hepatotoxicity associated with dietary supplements containing anabolic steroids. *Clin Gastroenterol Hepatol* 2007; **5**: 809–12.
168. Schwingel PA, Cotrim HP, Salles BR, *et al.* Anabolic-androgenic steroids: a possible new risk factor of toxicant-associated fatty liver disease. *Liver Int* 2011; **31**: 348–53.
169. Fasinu PS, Bouic PJ, Rosenkranz B. An overview of the evidence and mechanisms of herb-drug interactions. *Front Pharmacol* 2012; **3**: 69.
170. Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. *Br J Clin Pharmacol* 2012 [Epub ahead of print].
171. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998; **158**: 2200–11.
172. Zhou S, Gao Y, Jiang W, Huang M, Xu A, Paxton JW. Interactions of herbs with cytochrome P450. *Drug Metab Rev* 2003; **35**: 35–98.
173. Nowack R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John's Wort - and beyond!. *Nephrology (Carlton)* 2008; **13**: 337–47.
174. Yang SY, Juang SH, Tsai SY, Chao PD, Hou YC. St. John's wort significantly increased the systemic exposure and toxicity of methotrexate in rats. *Toxicol Appl Pharmacol* 2012; **263**: 39–43.