Journal of Medicinal Plants Studies

www.PlantsJournal.com

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Hepatotoxicity of herbal medicinal products

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Abstract
Plant remedies, despite their innocuity reputation, are implicated in adverse events. The present review focuses on 30 popular herbs which are associated with severe and sometimes fatal hepatotoxicity: *Actaea racemosa, Aloe barbadensis, Atractylis gummifera, Callilepsis laureola, Camellia sinensis, Centella asiatica, Chelidonium majus, Ephedra sinica, Garcinia cambogia, Hypericum perforatum, Larrea tridentata, Lycopodium serratum, Manihot esculenta, Mentha pulegium, Mitragyna speciosa, Morinda citrifolia, Piper methysticum, Polygala chinensis, Polygonum multiflorum, Psoralea corylifolia, Scutellaria biacalensis, Scutellaria lateriflora,* Senna (*Cassia acutifolia & Cassia angustifolia*), *Symphytum officinale, Teucrium chamaedrys, Teucrium polium, Usnea species, Valeriana officinalis, Xanthium strumarium* and some chinese herbal mixtures such as Sho-saiko-to.
Pharmacovigilance and tighter regulation are needed to prevent such cases.

Keywords: herbals, hepatotoxicity, pharmacovigilance

1. Introduction
Despite patient perceptions that herbal products are harmless, many of them have been reported to induce acute and chronic severe liver injury [1, 2].
People struggling with obesity seek herbal slimming aids and the number of those with acute hepatitis is on the rise [3-5].
The present review examines 30 herbs reported to cause hepatotoxicity:
Actaea racemosa, Aloe barbadensis, Atractylis gummifera, Callilepsis laureola, Camellia sinensis, Centella asiatica, Chelidonium majus, Ephedra sinica, Garcinia cambogia, Hypericum perforatum, Larrea tridentata, Lycopodium serratum, Manihot esculenta, Mentha pulegium, Mitragyna speciosa, Morinda citrifolia, Piper methysticum, Polygala chinensis, Polygonum multiflorum, Psoralea corylifolia, Scutellaria biacalensis, Scutellaria lateriflora, Senna (*Cassia acutifolia & Cassia angustifolia*), *Symphytum officinale, Teucrium chamaedrys, Teucrium polium, Usnea* species, *Valeriana officinalis, Xanthium strumarium* and some chinese herbal mixtures such as Sho-saiko-to.
Public and physicians should be alert to minimize the dangers of herbal product use.

Methods
Current literature on the hepatotoxicity of herbal drugs is reviewed**.**

Results
1. *Actaea racemosa*, *Cimicifuga racemosa*, cohosh, Ranunculaceae
Cimicifuga racemosa as anti-inflammatory agent, caused in two patient's acute elevation of liver enzymes and cholestasis [6].
A 60-year-old Caucasian lady taking black cohosh, underwent liver transplantation due to acute liver failure [7].

2. *Aloe barbadensis* Mill. Syn. and *Aloe vera* Tourn. Ex Linn (Liliaceae)
Ingestion of *Aloe vera* is associated with diarrhea, electrolyte imbalance, kidney dysfunction, and conventional drug interactions. A 35-year-old woman lost 5 L of blood during surgery as a result of such an interaction between Aloe vera and sevoflurane based on the antiplatelet effects of these 2 agents [8, 9].
A 21-year-old female patient on *Aloe vera* for four weeks was admitted to the hospital with toxic hepatitis [10].

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3. *Atractylis gummifera* L, Asteraceae

A 7-year old boy, in Greece, 2 days after ingestion of an extract from the plant's root was hospitalized, in coma stage II, with fatal hepatocellular damage and acute renal failure [11]. A 30-month-old boy was admitted in coma (Glasgow Coma Scale 8) after cutaneous application of *A. gummifera* L. on a skin burn with hepatic cellular injury, cholestasis, and increased creatinine. The child was discharged with residual renal insufficiency [12].

Intoxication by *Atractylis gummifera* L. happened in Morocco on a 12 year old child who accidentally ingested it. Precocious treatment saved him [13].

The toxicity of Atractylis gummifera resides in atractyloside and carboxyatractyloside, two diterpenoid glucosides capable of inhibiting mitochondrial oxidative phosphorylation. No specific pharmacological treatment for Atractylis gummifera intoxication is yet available and all the current therapeutic approaches are only symptomatic new therapeutic approaches could come from immunotherapy research: some studies have already tried to produce polyclonal Fab fragments against the toxic components of Atractylis gummifera [14].

4. Callilepsis laureola Asteraceae

Callilepis laureola, has been found to cause fatal liver necrosis in the Black population of Natal using it for self-medication or prescribed by herbalists and witchdoctors [15]

C. laureola cytotoxicity in human hepatoblastoma Hep G2 cells in vitro was assessed and the findings are in accordance with the observed hepatotoxicity in clinical cases of C. laureola poisoning [16].

The traditional Zulu remedy impila (Callilepis laureola) can cause acute fatal hepatocellular necrosis, especially in children [17].

The clinical and pathological features of toxic centrilobular zonal necrosis in Natal Blacks are described [18].

5. *Camellia sinensis* (green tea), L Theaceae

Green tea, obtained from the leaves of *Camellia sinensis* is suspected to induce hepatocellular liver damage with long latency and long recovery time of about 2 months. Liver injury associated with multicomponent preparations of green tea (ingredients interactions) were more serious with longer recovery time (10 months) and in some cases requiring liver transplantation [19].

A case of fulminant hepatitis during self-medication with Exolise (80% ethanolic dry extract of green tea) requiring liver transplantation has been reported [20].

A young healthy woman presented with fulminant hepatic failure requiring emergent liver transplantation caused by a dietary supplement and fat burner containing usnic acid and green tea [21].

There are a few articles in Spanish reporting cases of acute hepatitis induced by Camellia sinensis [22, 23, 24].

6. *Centella asiatica* Lin Urban, Apiaceae

Three women (61, 52 and 49 years old) developed jaundice, chronic and granulomatous hepatitis after taking *Centella asiatica* for 30, 20 and 60 days.

All patients improved with *Centella asiatica* discontinuation, and ursodeoxycholic acid 10 mg/kg/day. The first patient took *Centella asiatica* again, with recurrence of the damage. *Centella asiatica* contains pentacyclic triterpenic saponosides (asiaticoside, madecassoside and as other plants Germander, Skullcap and Glycyrrhizin containing di- or triterpenic active principles, can produce hepatic injury by promoting apoptosis and altering cell membranes [3, 25].

A 15 year old girl taking Gotu cola (*Centella asiatica*) bought over the Internet, for acne treatment, presented with acute hepatitis. She improved after treatment with N-acetylocysteine and vitamins [26].

7. *Chelidonium majus* L, Greater Celandine, Papaveraceae

Greater Celandine (*Chelidonium majus*) is a well-known herbal remedy frequently used for irritable bowel syndrome. Acute liver injury was reported in two patients, who fully recovered after the withdrawal of Greater Celandine [27].

There is striking evidence for herb-induced liver injury by Greater Celandine (*Chelidonium majus* L.) with high causality gradings and hepatotoxicity caused by an idiosyncratic reaction of the metabolic form, but there is uncertainty with respect to its culprit (s) [28].

In 16 patients from various European countries, herbal hepatotoxicity was of probable and highly probable causality for Greater Celandine, using the original and updated scale of CIOMS (Council for International Organizations of Medical Sciences). This is an acute clinical course exhibiting a hepatocellular pattern of injury and is correlated to an idiosyncratic reaction with its metabolic subtype. Jaundice combined with high values of serum aminotransferases was present in virtually all cases with favourable outcome despite severe clinical course.

There is uncertainty regarding the respective causative compound(s) among the 20 ingredients including various biologically active isoquinoline alkaloids. [29].

A 42-year-old woman developed jaundice due to acute hepatitis several weeks after ingestion of a herbal preparation containing greater celandine (*Chelidonium majus*) and curcuma root, which had been prescribed by an alternative therapist due to a skin complaint. After the medication had been withdrawn, clinical recovery was rapid and the hepatic functions returned to normal within 2 months.

The hepatitis was ascribed to the known hepatotoxic effects of *C. majus* [30].

A 46-year-old woman who had taken *Lycopodium similiaplex* solution as sedative for the previous 8 weeks, presented with hepatitis confirmed by liver biopsy. Discontinuing *L. similiaplex* use, liver values returned to normal and she was asymptomatic. The two constituents, *Lycopodium serratum* and *Chelidonium majus*, are found to be potentially toxic [31].

8. *Ephedra sinica* (Cao Ma Huang) Ephedraceae

Ephedra alkaloid use mainly in weight loss products, induces severe hepatic dysfunction and even features of fulminant hepatic failure evolving either death or transplantation with complications, in some of the cases.

The time interval of approximately 6 weeks or more between the use of the drugs containing ephedra, and the absence of hypersensitivity manifestations, suggest an idiosyncratic mechanism for liver injury [3, 5].

There is a report of acute hepatitis associated with the use of ma-huang, a chinese herbal product derived from plants of the Ephedra species [32, 33].

9. *Garcinia cambogia* L., Clusiaceae

Garcinia cambogia, a supplement widely promoted for weight loss caused acute liver failure and fulminant hepatic failure both cases requiring liver transplantation [33-35].

10. *Hypericum perforatum* L, Hypericaceae, St. John's wort

St John's wort (*Hypericum perforatum* L.), used for the treatment of mild to moderate clinical depression. Through its

active constituent's hypericin, pseudohypericin and hyperforin, it can induce both intestinal and hepatic CYP3A4 enzyme with the potential of drug interactions [36].

A case of liver damage in an elderly patient after the use of herbal products of Hypericum perforatum and copaiba (Copaifera langsdorffii Desf), with clinical recovery of the patient after discontinuing their use, is reported [37].

There are clinical reports in the literature describing Hypericum perforatum, as the causative agents of hepatotoxicity [38].

11. *Larrea tridentata* DC, Zygophyllaceae Coville, chaparral, Creosote bush

There are data indicating that the use of chaparral may be associated with jaundice, cholestatic hepatitis, acute to chronic irreversible liver damage with progression to cirrhosis or fulminant hepatic failure that required liver transplants [39].

Several case reports have demonstrated high doses of Larrea-containing herbals induce hepatotoxicity and nephrotoxicity in humans due to nordihydriguaiaretic acid administration of which is lethal in the mouse (LD(50)=75 mg/kg) [40].

The potent antioxidant nordihydroguaiaretic acid was widely used during the 1950s as a food preservative. Later it was banned after reports of toxicity during the early 1960s [41].

12. *Lycopodium serratum* L, Jin Bu Huan, Lycopodiaceae

A single, acute ingestion of jin bu huan in children rapidly produced life-threatening neurologic and cardiovascular manifestations, while long-term use in adults was associated with hepatitis. Jin bu huan contains levo-tetrahydropalmatine, a potent neuroactive substance [42].

Jin Bu Huan can cause liver injury due to hypersensitive or idiosyncratic reactions or direct toxicity to active metabolites. Reusing Jin Bu Huan caused abrupt recrudescence of hepatitis [43].

A 46-year-old woman who had taken Lycopodium similiaplex Solution as sedative for the previous 8 weeks, presented with hepatitis confirmed by liver biopsy. Discontinuing L. similiaplex use, liver values returned to normal and she was asymptomatic. The two constituents, Lycopodium serratum and Chelidonium majus, are found to be potentially toxic [31].

13. *Manihot esculenta*, Grantz, Euphorbiaceae, cassava

Cassava (*Manihot esculenta* Crantz) is one of the world's most cultivated and consumed plants after maize and rice in most regions of South America, Africa, and Asia. However, it is also characterized by the presence in its roots of potentially toxic hydrocyanic acid [44].

Cassava (*Manihot esculenta* Crantz) is a major source of dietary energy for humans and domestic animals in many tropical countries. However, consumption of cassava is limited by its characteristic content of cyanogenic glycosides [45].

Tropical ataxic neuropathy, causes significant disability as well as increased mortality with a strong geospatial endemic prevalence in areas of cassava cultivation [46].

Cyanide in cassava is associated with high case-fatality ratios neurologic diseases [47].

There were significant increases ($P < 0.05$) in total and free cyanide and thiocyanate in in the liver, kidney, and heart of male albino rats fed a diet containing yellow cassava for 7 to 28 days with significant increases ($P<0.05$) in serum glucose, alanine aminotransaminase and aspartate aminotransaminase [48].

Cassava diet, common in sub-Saharan Africa and parts of Asia causes liver cancer [49].

Sub-Saharan populations commonly consume food contaminated by mycotoxins, particularly aflatoxins (predominantly found in peanut, maize, rice, and cassava) and fumonisins, which occur primarily in maize. Aflatoxin promotes hepatocellular cancer, and fumonisin may promote esophageal cancer [50]. Studies have linked aflatoxins (in ground nuts, cassava) to hepatocellular carcinoma [51].

14. *Mentha pulegium* L, Lamiaceae, Pennyroyal

Pennyroyal, ingested as an abortifacient among other uses, has been associated with severe hepatotoxicity and death. Studies with its stable isotope labeled metabolites, pulegone and menthofuran proved that these compounds are metabolized via hepatic cytochrome P450 to toxic intermediates [52].

In an animal model, the combination of P450 inhibitors cimetidine and disulfiram significantly mitigates the effects of pennyroyal toxicity and does so more effectively than either agent alone. These data suggest that R-(+)-pulegone metabolism through CYP1A2 appears to be more important in the development of a hepatotoxic metabolite than does metabolism viaCYP2E1 [53].

Hepatic and neurologic injury developed in two infants after ingestion of mint tea that contained the toxic agent pennyroyal oil and its toxic constituents, including pulegone and its metabolite menthofuran. Fulminant liver failure with cerebral edema and necrosis developed in the first infant, who died. This infant was positive only for menthofuran (10 ng/mL). In the other infant, who was positive for both pulegone (25 ng/mL) and menthofuran (41 ng/mL), hepatic dysfunction and a severe epileptic encephalopathy developed [54, 55].

15. *Mitragyna speciosa* Korth Havil, Rubiaceae

Mitragyna speciosa (better known as ketum), is a popular medicinal plant in Southeast Asia which is commonly used for its morphine-like effects, its ability to ameliorate withdrawal signs after abrupt cessation of opioid abuse and to prevent fatigue from working under hot tropical weather. It was demonstrated in rats that mitragynine, the principal alkaloid of *Mitragyna speciosa* leaves, is relatively safe at lower sub-chronic doses (1-10mg/kg) but exhibited toxicity at a highest dose (sub-chronic 28 days: 100mg/kg). This was confirmed by liver, kidney, and brain histopathological changes, as well as hematological and biochemical changes [56, 57].

Mitragyna speciosa Korth (ketum) is used in Malaysia for treating diarrhea, worm infestations and also as analgesic and antipyretic. Oral administration of standardized methanolic extraction of Mitragyna speciosa Korth resulted in increasing rat blood pressure after an hour of drug administration. The highest dose of extract also induced acute severe hepatotoxicity and mild nephrotoxicity [58].

16. *Morinda citrifolia* L, Noni, Rubiaceae

NONI juice (*Morinda citrifolia*) is a popular wellness drink.

In two cases causality of liver injury by NONI juice was asses-sed. Routine laboratory tests and transjugular or percutaneous liver biopsy were performed. The first patient underwent successful liver transplantation while the second patient recovered spontaneously after cessation of NONI juice.

A 29-year-old man with previous toxic hepatitis associated with small doses of paracetamol developed sub-acute hepatic

failure following consumption of 1.5 L NONI juice over 3 wk necessitating urgent liver transplantation.

A 62-year-old woman without evidence of previous liver disease developed an episode of self-limited acute hepatitis following consumption of 2 L NONI juice for over 3 months. The most likely hepatotoxic components of Morinda citrifolia were anthraquinones [59].

A case of a 14-year-old previously healthy boy with acute hepatotoxicity after noni berry juice consumption was reported [60].

Two cases of hepatotoxicity related to the consumption of noni juice (morinda citrifolia) the one required liver transplantation [61].

A 38-year-old woman developed acute liver injury associated with noni juice consumption on a long-term (9 months) anticonvulsant therapy. Clinical presentation and liver biopsy were consistent with severe, predominantly hepatocellular type of injury. Both agents were stopped and corticosteroids were initiated. Five months later the patient had fully recovered [62].

A 45-year-old patient with highly elevated transaminases and elevated lactate dehydrogenase with unremarkable medical history, no medication on regular basis, no evidence for viral hepatitis, Epstein-Barr virus or cytomegalovirus, autoimmune hepatitis, Budd-Chiari syndrome, haemochromatosis or Wilson's disease. For 'prophylactic reasons' he had been drinking the juice of Noni (*Morinda citrifolia*), during the preceding 3 weeks. Herbal toxicity, which was confirmed by a liver biopsy. After ceasing the ingestion of Noni, transaminase levels normalized quickly and were within normal ranges 1 month after the first presentation [63].

17. *Piper methysticum* G. Forst. Piperaceae, Kawa
Kava derived from the root of Piper methysticum, is used as an antianxiety and sedative extract. Kawa components such as kavalactones, pipermethystine and flavokavain B have been demonstrated as hepatotoxic. The mould hepatotoxin aflatoxin is a likely cause of kava hepatotoxicity, but it remains more likely that chemical constituents of kava are the cause of the hepatotoxicity from kava [64].

Kava was one of the top 10 selling herbal remedies in Europe and North America before the reports of its hepatotoxicity. This adverse effect did not happen with the traditional beverage which was prepared as a water infusion in contrast to the commercial products which are extracted with organic solvents. Kavalactones, the active principles in kava, are potent inhibitors of several of the CYP 450 enzymes, and also block GABA receptors and sodium and calcium ion channels [36].

Kawa products have been associated with liver injuries in Western countries and the FDA urged report of any such case [65].

A previously healthy 14-year-old female was admitted to the hospital with hepatic failure following the use of kava kava for four months. Initial therapy, including plasmapheresis, was unsuccessful and she deteriorated. She ultimately required a liver transplant and now remains well. The liver biopsy showed hepatocellular necrosis consistent with chemical hepatitis. A work-up for alternative causes of liver failure was negative [66].

In a case, high concentrations of kavalactones and ethanol were detected in post mortem femoral blood. An injection needle with a 10-mL syringe containing 7.5 mL of slightly yellowish liquid was found next to the victim, and there were numerous needle prints on both lower arms following the venous tracks. No evidence of other cause of death was found in the medico-legal investigation. The case was therefore classified as suicide using an injection of kavalactones intravenously together with alcohol poisoning [67].

18. *Polygala chinensis* L, Polygalaceae
Polygala chinensis (milkworts, snakeroots) known to induce milk production in animals is reported to cause toxic hepatitis [68].

19. *Polygonum multiflorum*, Polygonaceae, Shou Wu Pian
Ethanol extracts of Polygonum multiflorum, can cause fatty liver disease by decreasing β-oxidation of fatty acid and increasing lipogenesis [69].

A case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from Polygonum multiflorum [70].

Cholestatic hepatitis developed in a Chinese woman taking a Shou Wu Pian preparation for the greying of her hair, and liver biopsy was consistent with a toxic reaction. Clinical and biochemical resolution occurred following cessation of the drug [71].

20. *Psoralea corylifolia*, Fabaceae, Boh-Gol-Zhee
A postmenopausal woman used the seeds of Psoralea corylifolia in amounts over 10 times the usual dose for the treatment of osteoporosis. She presented with acute cholestatic hepatitis. Liver biopsy showed zone three necroses, degenerating cells, cholestasis, and infiltrations with inflammatory cells [72].

21. *Scutellaria biacalensis* L, Lamiaceae Chinese skullcap, Black Catechu?
A dietary supplement to comfort sore joints and improve flexibility and mobility containing Chinese skullcap caused hepatotoxicity in two patients resolved after discontinuation of the supplement. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6 for both patients) between the patients' development of hepatotoxicity and the supplement [73].

A patient developed drug induced liver injury following the intake of Chinese skullcap in an over-the-counter arthritis supplement. There was a strong temporal association between the intake of supplement and onset of symptoms, and also pulmonary infiltrates simultaneously with the hepatotoxicity. Both the hepatic and pulmonary complications completely resolved over few weeks after the patient stopped taking the medication [74].

A woman presented withsignificant cholestasis and hepatitis following consumption of the herb Chinese skullcap. She was significantly improved after discontinuation of the supplement. Liver biopsy at that time was consistent with acute drug induced liver injury [75].

22. *Scutellaria lateriflora*, Lamiaceae
Scutellaria lateriflora (skullcap) is used in insomnia and anxiety. Cases of hepatotoxicity have been reported due to intentional or unintentional adulteration, with the potentially hepatotoxic *Teucrium* spp., *T. canadense* and *T. chamaedrys* [76].

23. Senna (*Cassia acutifolia* & *Cassia angustifolia*)
Cassia acutifolia and angustifolia plants are widely used as laxatives. Their chronic abuse may cause chronic diarrhea with fluid and electrolyte loss. Severe hepatotoxicity is rare

and could be explained by the exposure of the liver to toxic metabolites of anthraquinone glycosides (sennosides). A 52-year-old woman taking for >3 years, one liter of a tea each day made from 70 g of dry senna fruits, developed acute hepatic failure and renal impairment requiring intensive care therapy. The severity of the hepatic failure was reflected by the increase in prothrombin time (international normalized ratio >7) and the development of encephalopathy. Liver transplantation was discussed, but the patient ultimately recovered with supportive therapy. Renal impairment was consistent with proximal tubular acidosis, also with marked polyuria refractory to vasopressin administration. Suprisingly, large amounts of cadmium were transiently recovered in the urine [77].

24. *Symphytum officinale*, Comfrey
Comfrey has been used as a vegetable and herbal remedy by humans. It is a rat liver toxin and carcinogen and studies in the transgenic Big Blue rat model, indicated that comfrey is mutagenic in rat liver and its tumorigenicity results from the genotoxicity of pyrrolizidine alkaloids in the plant [78, 79].

A woman 47 years old consuming 10 caps comfrey tea a day, from 1978 to1982 developed ascites and veno- occlusive disease [80].

Comfrey and herbal remedies containing Pyrrolizidine Alkaloids can induce hepato- sinusoidal obstruction syndrome or veno-occlusive disease. Preventing overdose and monitoring long-term use of such remedies may avoid glutathione depletion leading to mitochondrial injury. Moreover, immediately stopping the herbal medication prevents further harm to the liver. Chronic consumption of hepatotoxicants can lead to cancer formation and promotion [81].

25. *Teucrium chamaedrys* L, Lamiaceae
Teucrium chamaedrys L is popular as a slimming decoction. Hydroalcoholicextracts are used as flavourings in the preparation of wines, bitters and liqueurs. Teucrin A and teuchamaedryn A are the major hepatotoxic components of the diterpenoid fraction of *T. chamaedrys* L. Two recurrent cases of severe acute liver injury are attributed to the use of a wild germander decoction. This was prepared with some variation in traditional family method (without negative consequences) and the decoction taken by the patients with higher concentration of teucrin A [82, 83].

In two cases of acute hepatitis after consuming for several months a tea of *Teucrium chamaedrys* (germander), after ruling out other causes of hepatitis, we consider that Teucrium chamaedrys provoked the disease. One patient presented acute, cholestatic hepatitis and another presented mixed (hepatocellular and cholestatic) hepatitis. In both patients, the disease was resolved after discontinuing the intake of the herbal tea [84].

Germander was marketed in France starting in 1986 and widely used for weight control, but was then banned after reports of hepatotoxicity including acute and chronic hepatitis and liver failure; mechanism of injury appears to be metabolic activation to a toxic intermediate [furan-containing neoclerodane diterpenoids [85].

Seven cases of germander hepatotoxicity from France; 6 women and 1 man, aged 15 to 56 years, developing jaundice after taking germander capsules or tea for 3 to 18 weeks [bilirubin 4.0- 27.7 mg/dL, ALT 9-61 times ULN, Alk P 0.5-3 times ULN], resolving in 1.5 to 6 months; 3 were re exposed and all had recurrence with jaundice, all ultimately recovered

[86].

Two French women, 28 and 56 year old, developed jaundice 6-12 weeks after starting germander [bilirubin 3.0-9.6 mg/dL, ALT 35-45 times ULN, Alk P 0.6-1.4 times ULN], resolving in 4-10 weeks, recurrence in one patient 3 weeks after restarting [87].

Teucrin A, one of the major furanoneocleradane diterpenes of the herbal plant germander was found to cause the same midzonal hepatic necrosis in mice, as observed with extracts of the powdered plant material. Hepatotoxicity of teucrin A also was increased following pretreatment with the inhibitor of glutathione synthesis buthionine sulfoximine. Most importantly, the tetrahydrofuran analog of teucrin A, obtained by selective chemical reduction of the furan ring, was not hepatotoxic, a result that provides strong evidence that oxidation of the furan ring moiety of the neoclerodane diterpenes is involved in the initiation of hepatocellular injury caused by germander [88].

26. *Teucrium polium* L, Lamiaceae, wall germander
Teucrium polium grows mostly in the Mediterranean basin and is popular, because of hypoglycemic and hypolipidemic properties. Two Greek female patients, who used the plant's extract to control the cholesterol levels presented with very high aminotransferases after consuming herbal tea for 2 or 3 months. One patient also developed jaundice. Histologic examination of liver biopsies showed hepatitis with moderate or severe necroinflammatory activity. Discontinuation of the herbal remedy resulted in normalization of the liver enzymes in both patients.

Our findings, and those of other authors, suggest that T. polium may not be safer than T. chamaedrys and T. capitatum, which have also been reported to occasionally cause hepatotoxicity [89].

A *70 year old woman developed jaundice after 3 months of taking a Teucrium polium extract [bilirubin 38 mg/dL, ALT 1321 U/L, Alk P 318 U/L, AMA 1:160], resolving in 3 weeks and AMA becoming negative).[90]*

A case of acute hepatitis in a 70-year-old farmer, using Teucrium polium (golden germander) as hypoglycaemic aid. The patient presented only with jaundice, after 1 month's consumption of large quantities of this herb in a tea form [91].

27. *Usnea species* (Dill) Adams Parmeliaceae
Usnic acid has been shown to kill hepatocytes, a recent report describes acute liver failure requiring liver transplantation in a patient who took pure usnic acid [3, 5, 21].

28. *Valeriana officinalis* L Caprifoliaceae
The Berlin Case-Control Surveillance Study in more than 180 Departments of all 51 Berlin hospitals from October 2002 to December 2011, supports the suspected association between Valeriana use and liver injury and the predominant pattern of liver injury was hepatocellular [92].

A 50-year-old Caucasian woman admitted with abnormal liver biochemistry in a routine blood examination, otherwise asymptomatic. She had consumed tea with valeriana herb for 3 weeks (5 cc extract of valerian root thrice weekly) and 10 tablets of vaimane, an over-the-counter medication containing 125 mg dry valerian extract in each tablet, 2 months before [93, 94].

29. *Xanthium strumarium* L Asteraceae, Cang-Er-Zi
The fruit of *Xanthium strumarium* L. (Cang-Er-Zi) is a traditional Chinese medicine used in nasal diseases and

headache according to the *Chinese Pharmacopoeia.* The two kaurene glycosides (atractyloside and carbxyatractyloside), the main toxic constituents isolated from Fructus Xanthii induce hepatotoxicity in mice *via* induction of oxidative stress as lipid peroxidation in liver, with increased hepatic malondialdehyde concentration, as well as decreased superoxide dismutase, catalase activities and glutathione concentration [95].

An integrated metabonomics study, using high-resolution nuclear magnetic resonance in rats, demonstrated that the major hepatotoxicity constituents of Xanthium strumarium are atractyloside, carboxyatractyloside and 4'-desulphate-atractyloside, and mitochondrial inability, fatty acid metabolism, and some amino acids metabolism are involved [96].

Four cows died while grazing on a riverbank in South Africa, where mature cocklebur (Xanthium strumarium) was growing. Clinical signs were recumbency, apparent blindness, hypersensitivity to convulsive seizures and microscopic lesions were centrilobular to midzonal hepatocyte necrosis and hemorrhage. Based on all the data, X. strumarium poisoning in the herd of cattle was confirmed [3, 97].

A 25-year-old, previously healthy, woman presented to emergencies with altered mental status and an episode of tonic colonic seizure 7 days after drinking of a decocting plant preparation. She was respon*sive* only to pain stimuli Laboratory data were hypoglycemia, prolonged coagulation profiles, elevated liver and kidney enzymes, hepatomegally, diffuse hyper-echoic changes in liver and mild ascites. After three hours of conservative treatment by IV Dextrose, she was completely conscious and she revealed she was interested in having child, her medical follow up could not solve her childlessness problem, so an herbal medicine expert had suggested drinking an unknown herb after decocting in water once a day (each aliquot has a dry weight about 30-40 gm).Her husband brought the plant to the hospital and it proved to be Xanthium strumarium. The patient discharged on 7th day of admission. Her liver enzymes became normal within 3 months. She never used the plant againShe is still living in a small village and adopted a beautiful boy as one's own child [98].

30. Sho- saiko- to, Xiao- Chai –Hu- Tang
Sho- saiko- to is an extract of seven Chinese herbs. It is suggested to have hepatoprotective properties e.g. to help prevent liver cancer in patients with cirrhosis [99].
However a 52 year old woman is reported with acute hepatitis after continual consumption of the decoction of Xiao- Chai –Hu- Tang, for 1.5 months (all viral hepatitis markers negative).She improved after discontinuing the herb, liver biochemical tests normalized 2 months later [100].

Results-Discussion
The documented toxicity of the reported plant remedies emphasizes the importance of pharmacovigilance for consumers and healthcare providers and quality control in the manufacture of these products. Clinicians should always inquire about herbal products intake in cases of unexplained liver injury

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