



Chinese and other Asian Herbal Medicines

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OVERVIEW

Among the more than 7000 Chinese herbal medications, only a few have been linked to episodes of clinically apparent liver injury, most commonly mentioned being Ba Jiao Lian, Chi R Yun, Jin Bu Huan, Ma Huang/ Ephedra, and Shou Wu Pian. Many of these are mixtures of herbs and the composition can vary considerably despite an identical name. In other instances, the composition of the herbal mixture is totally unknown. Traditional Chinese herbal medicines are widely used in Asian communities throughout the world for a broad array of conditions. Many of these are harmless or have only minor and transient adverse effects. A few can cause hepatic injury when given in high concentrations, and some even when used in recommended doses.

Approach to Hepatotoxicity in Patients Taking an Herbal Medicine

When evidence of liver injury arises in a patient taking a traditional herbal medication, the appropriate response is to stop the agent and attempt to identify its nature and components. A major problem is that multiple herbs are often being taken and their exact nature and even name may not be known. The herbal products are often poorly labeled as to their composition and they may be mislabeled or contaminated with toxins, bacteria, metals or even conventional, synthetic or semisynthetic medications such as nonsteroidal antiinflammatory agents, corticosteroids, fibrates, or statins. It is helpful to collect the residual pills or extract as they may be helpful if identification is necessary. Characterization of the clinical phenotype or pattern of hepatic injury is also helpful in identifying the specific agent causing the injury. For instance, comfrey and plant pyrrolizidine alkaloids are typically associated with acute sinusoidal obstruction syndrome, whereas germander, greater celandine, usnic acid, Jin Bu Huan, Shou Wu Pian and Ma Huang (ephedra) present typically with an acute viral hepatitis-like syndrome. Pennyroyal oil and Chi R Yun (Breynia) cause acute hepatic necrosis, often accompanied by signs and symptoms of injury to other organs, such as the gastrointestinal tract, lungs, kidneys or central nervous system. Androgenic steroids cause bland cholestasis, characterized by deep jaundice and pruritus with minimal elevations in serum aminotransferase and alkaline phosphatase levels. In all situations, other causes of acute liver injury need to be excluded.

Specific Chinese and other Asian herbal medications implicated in liver injury include: Ba Jiao Lian* (Dysosma pleianthum), Bol Gol Zhee (Fructus psoraleae), Chi R Yun* (Breynia officinalis), Jin Bu Huan* (Lycopodium serratum), Ma Huang (Ephedra)*, Sho Saiko To*, and Shou Wu Pian* (Polygonum multiflorum). However, in many situations, the specific herbal product that is responsible for the liver injury is unclear and the injury ascribed to "Chinese Herbs" without specifying which.

References are given with each specific agent (*a drug record is in LiverTox), and selected general references to hepatotoxicity of miscellaneous and unspecified Chinese and Asian herbs are given in the Annotated Bibliography below.

Drug Class: Herbal and Dietary Supplements

Herbals in the Subclass Chinese and Other Asian Herbal Medicines: Ba Jiao Lian, Bol Gol Zhee, Chi R Yun, Jin Bu Huan, Ma Huang/Ephedra, Polygonum Multiflorum, Sho Saiko To and Dai Saiko To

ANNOTATED BIBLIOGRAPHY

References updated: 25 May 2022

- Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.
- (Expert review of hepatotoxicity published in 1999; hepatotoxicity of Chinese herbal products and teas are discussed generally without focus on any specific product or herb).*
- Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.
- (Review of hepatotoxicity of herbal and dietary supplements [HDS]; traditional Chinese and other Asian herbal medicines and teas are discussed, including Ma Huang, Shou Wu Pian, Ba Jiao Lian, Jin Bu Huan, Breynia and Syo-Saiko-To).*
- PDR for Herbal Medicines. 4th ed. Montvale, New Jersey: Thomson Healthcare Inc. 2007.
- (Compilation of short monographs on herbal medications and dietary supplements including sections on Ma Huang and other Chinese herbals).*
- Mokhobo KP. Herb use and necrodegenerative hepatitis. S Afr Med J. 1976;50:1096–9. PubMed PMID: 959916.
- (12 African patients from Lesotho, ages <5 to 46 years, presented with ascites, edema or jaundice after taking herbal medications, toxic herb most likely Senecio species; 7 died and two others had cirrhosis and chronic symptoms).*
- Sinniah D, Baskaran G. Margosa oil as a cause of Reye's syndrome. Lancet. 1981;1:487–9. PubMed PMID: 6110100.
- (13 Malaysian children with margosa oil poisoning, with onset of vomiting within a few minutes of taking the herbal medicine, presented with drowsiness and metabolic acidosis, liver tests being usually normal, but liver biopsy showing steatosis of liver and renal tubules with mitochondrial damage suggestive of Reye syndrome).*
- Sinniah D, Baskaran G, Looi LM, Leong KL. Reye-like syndrome due to margosa oil poisoning: report of a case with postmortem findings. Am J Gastroenterol. 1982;77:158–61. PubMed PMID: 7081175.
- (4 month old Indian female developed vomiting 1 hour after second ingestion of margosa oil [for cough], with drowsiness and acidosis [pH 6.8, bilirubin 0.2 mg/dL, AST 170 U/L, ALT 44 U/L, CPK 3180 U/L, prothrombin 16%], liver biopsy on day 5 showing microvesicular fat and mitochondrial abnormalities; died of cerebral edema on day 10).*
- Editorial. Pyrrolizidine alkaloids. Lancet. 1984;1:201–2. PubMed PMID: 6141340.
- (Plants have evolved poisons that are toxic to insects, but can also cause hepatic venoocclusive disease in grazing animals and in humans who ingest them in teas and herbal medications: “a disastrous discontinuity of tradition”).*
- Ridker PM, Ohkuma S, McDermott WV, Trey C, Huxtable RJ. Hepatic veno-occlusive disease associated with the consumption of pyrrolizidine-containing dietary supplements. Gastroenterology. 1985;88:1050–4. PubMed PMID: 3972224.

- (49 year old woman developed ascites and edema 6 months after starting comfrey tea and capsules, requiring portocaval shunt and having slow improvement after stopping).
- Kumana CR, Ng M, Lin HJ, Ko W, Wu PC, Todd D. Herbal tea induced hepatic veno-occlusive diseases; quantification of toxic alkaloid exposure in adults. *Gut*. 1985;26:101–4. PubMed PMID: 3965360.
- (Four young women brewed Indian herbal tea to treat psoriasis and 3 developed ascites from sinusoidal obstruction syndrome 19–45 days later [bilirubin 0.6, 0.6 and 3.3 mg/dL, ALT 63, 122 and 69 U/L], one dying of hepatic failure; analysis of tea revealed pyrrolizidine alkaloids).
- Culvenor CCJ. Pyrrolizidine alkaloids: some aspects of the Australian involvement. *Trends Pharmacol Sci*. 1985;6:18–22.
- (Presence of pyrrolizidine alkaloids in several common Australian weeds is a health hazard to livestock and humans; these include *Heliotropium europaeum*, *Echium plantagineum*, *Senecio* and *Crotalaria* species).
- Mizoguchi Y, Miyajima K, Sakagami Y, Yamamoto S. *Nippon Naika Gakkai Zasshi*. 1986;75:1453–6. [A severe case of drug-induced allergic hepatitis in herbal medicine]. Japanese. PubMed PMID: 3805846.
- (A 27 year old developed jaundice 6 weeks after taking Kinshigan, a Kampo herb with rapid recovery upon stopping, but recurring with a more severe course 2 weeks after restarting [bilirubin 28.5 mg/dL, ALT 166 U/L, Alk P 1.5 times ULN, 1% eosinophils]; among 18 ingredients, *Scutellariae radix*).
- Satake I, Maeda M, Koyama W, Sakamoto S, Koizumi S, Kanayama M. A case of hepatic injury caused by an herb drug. *Acta Hepatol Jpn*. 1986;27:238–41.
- Koga Y, Yoshida I, Kimura A, Yoshino M, Yamashita F, Sinniah D. Inhibition of mitochondrial functions by margosa oil: possible implications in the pathogenesis of Reye's syndrome. *Pediatr Res*. 1987;22:184–7. PubMed PMID: 3658544.
- (Studies of isolated rat mitochondria demonstrated that margosa oil is a mitochondrial toxin, uncoupling respiratory chain enzymes and depleting ATP).
- Sinniah R, Sinniah D, Chia LS, Baskaran G. Animal model of margosa oil ingestion with Reye-like syndrome. Pathogenesis of microvesicular fatty liver. *J Pathol*. 1989;159:255–64. PubMed PMID: 2593049.
- (In mice, margosa oil causes rapid onset of mitochondrial injury, steatosis and glycogen depletion).
- Georgiou M, Sianidou L, Hatzis T, Papadatos J, Koutselinis A. Hepatotoxicity due to *Atractylis gummifera*-L. *J Toxicol Clin Toxicol*. 1988;26:487–93. PubMed PMID: 3230599.
- (7 year old Greek child developed abdominal pain, vomiting and progressive obtundation 2 days after being given an extract made from roots of *Atractylis gummifera*, dying in coma 8 days later [bilirubin rising to 9.8 mg/dL, ALT 6000 U/L], autopsy showing massive hepatic necrosis without steatosis).
- MacGregor FB, Abernethy VE, Dahabra S, Cobden I, Hayes PC. Hepatotoxicity of herbal remedies. *BMJ*. 1989;299:1156–7. PubMed PMID: 2513032.
- (Four cases of hepatitis attributed to herbals, all women, ages 41–57, developed jaundice 2 to 8 weeks after starting herbals for stress [“Neurelax” and “Kalms”] believed to contain skullcap and/or valerian [bilirubin 13.5–28.3 mg/dL, ALT 293–1165 U/L, Alk P 97–730 U/L], resolving 2–19 months after stopping).
- Carlsson C. Herbs and hepatitis. *Lancet*. 1990;336:1068. PubMed PMID: 1977040.
- (Analysis of laboratory results from 395 patients found higher average ALT levels among 53 patients taking herbals [55 U/L] than among those who did not [12 U/L]).
- Allen BR, Parkinson R, Hollman A, Jones R, Harper JI, Davies, Pollock I, Steel HM. Chinese herbs for eczema (letters). *Lancet*. 1990;336:177.

- (Series of letters concerning use of Chinese herbs for eczema; Allen pointing out the adulteration with corticosteroids; Hollman requesting the names of the herbs included in the mix; Harper providing a list of the herbs in the mixture; finally Davies describing a 9 year old girl who developed jaundice after taking this herbal mixture for 6 months [bilirubin 7.9 mg/dL, ALT 1950 U/L, Alk P 379 U/L], resolving within 2 months of stopping and recurring within one month of restarting).*
- Marutani K, Matsuo S, Nishijima T, Watanobe T, Ishida Y, Sasaki K, Kameda C, Itoh S. Light and electron microscopic findings in the liver of five patients with syo-saiko-to-induced hepatitis. *Jpn J Gastroenterol.* 1990;87:640.
- Beuers U, Spengler U, Pape GR. Hepatitis after chronic abuse of senna. *Lancet.* 1991;337:372–3. PubMed PMID: 1671276.
- (26 year old nurse taking high doses of senna alkaloids developed jaundice and pruritus [bilirubin not given, ALT 303 U/L, Alk P 227 U/L], resolving within a few weeks of stopping and recurring upon restarting [ALT >280 U/L]).*
- Miskelly FG, Goodyer LI. Hepatic and pulmonary complications of herbal medicines. *Postgrad Med J.* 1992;68:935. PubMed PMID: 1494520.
- (77 year old woman developed fatigue followed by jaundice 6 months after starting a herbal product with comfrey and skullcap [bilirubin 3.5 mg/dL, AST 520 U/L, Alk P 390 U/L], resolving within 6 months of stopping).*
- Graham-Brown R. Toxicity of Chinese herbal remedies. *Lancet.* 1992;340(8820):673–4. PubMed PMID: 1355233.
- (51 year old man took unknown Chinese herbs for psoriasis for 8 weeks and developed abnormal liver tests [bilirubin 1.6 mg/dL, ALT 2034 U/L, Alk P 348 U/L], resolving rapidly upon stopping).*
- Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. *Lancet.* 1992;340:674. PubMed PMID: 1355235.
- (28 year old woman developed jaundice 3-4 months after starting Chinese herbs for eczema, resolving upon stopping, but recurring with acute liver failure 2-3 weeks after restarting; the mixture containing 8 different herbal components).*
- Kao WF, Hung DZ, Tsai WJ, Lin KP, Deng JF. Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. *Hum Exp Toxicol.* 1992;11:480–7. PubMed PMID: 1361136.
- (5 patients with Bajiaolian toxicity presenting with nausea, diarrhea, abdominal pain, abnormal liver tests [bilirubin normal, ALT 43-66 U/L, AST 52-183, Alk P usually normal], thrombocytopenia, sensory and motor neuropathy consistent with podophyllotoxin intoxication).*
- Sheehan MP, Atherton DJ. One year follow-up of children with atopic eczema treated with traditional Chinese medicinal plants. *Br J Dermatol.* 1994;130:488–93. PubMed PMID: 8186115.
- (Among 37 children with eczema treated with Chinese herbs for up to 12 months, 2 developed asymptomatic AST elevations [315 and 586 U/L] with normal bilirubin [0.4 and 1.1 mg/dL], resolving within 8 weeks of stopping).*
- Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med.* 1993;328:246–52. PubMed PMID: 8418405.
- (Among 1539 adults interviewed by telephone, 34% used an unconventional therapy during the previous 12 months, including 3% using herbal medicines).*
- Centers for Disease Control and Prevention (CDC). Jin bu huan toxicity in children--Colorado, 1993. *MMWR Morb Mortal Wkly Rep.* 1993;42(33):633–6. PubMed PMID: 8350855.

(3 children, ages 13, 23 and 30 months, ingested 7, 17 and 60 tablets of Jin Bu Huan, developing lethargy and abnormal breathing within 30-60 minutes, responding rapidly to gastric lavage, activated charcoal and a cathartic, no mention of liver injury).

Centers for Disease Control and Prevention (CDC). Jin bu huan toxicity in adults--Los Angeles, 1993. MMWR Morb Mortal Wkly Rep. 1993;42(47):920-2. PubMed PMID: 8232178.

(3 women, ages 24, 45 and 66 years, taking Jin Bu Huan for insomnia for 2 to 4 months developed nausea, fatigue, pruritus and jaundice [bilirubin 0.7, 28.0 and 3.4 mg/dL, ALT 786, 1468 and 1308 U/L, Alk P 169, 133 and 225 U/L], resolving in 3-9 weeks upon stopping; analysis showed levo-tetrahydropalmatine which is not present in the plant claimed on the label [Polygala chinensis]).

Perharic L, Shaw D, Colbridge M, House I, Leon C, Murray V. Toxicological problems resulting from exposure to traditional remedies and food supplements. Drug Saf. 1994;11:284-94. PubMed PMID: 7848547.

(Retrospective and prospective survey identified 1070 enquires following exposure to herbal products, including 4 cases of liver injury from Chinese herbs, Psoralea coryliflora, valerian and skullcap).

Pillans PI, Eade MN, Massey RJ. Herbal medicine and toxic hepatitis. N Z Med J. 1994;107:432-3. PubMed PMID: 7970342.

(37 year old woman with psoriasis developed fatigue 13 days after starting Chinese herbs [bilirubin 0.6 rising to 7.9 mg/dL, ALT 243 to 2300 U/L, Alk P 234 to 380 U/L], with resolution within 7 weeks of stopping).

Caldwell SH, Feeley JW, Wieboldt TF, Featherston PL, Dickson RC. Acute hepatitis with use of over-the-counter herbal remedies. Va Med Q. 1994;121:31-3. PubMed PMID: 8142493.

(53 year old woman developed jaundice 4 weeks after starting an herbal for sleep [containing skullcap and valerian: 4 capsules nightly, with bilirubin 9 mg/dL, ALT 1208 U/L, Alk P 298 U/L, protime 13.5 sec], resolving in 3 months: Case 1 for skullcap).

Woolf GM, Petrovic LM, Rojter SE, Wainwright S, Villamil FG, Katkov WN, Michieletti P, et al. Acute hepatitis associated with the Chinese herbal product Jin Bu Huan. Ann Intern Med. 1994;121:729-35. PubMed PMID: 7944049.

(Seven adults developed hepatotoxicity due to Jin Bu Huan; 6 women and 1 man, ages 24 to 66 years, taking Jin Bu Huan for 7 to 52 weeks developed fever, fatigue, nausea, and pruritus with [n=3] or without jaundice [peak bilirubin 0.4 to 28.0 mg/dL, ALT 192 to 2149 U/L, Alk P 60 to 552 U/L], resolving in 2 to 30 weeks; this series included cases described by Woolf [1993]).

Delbanco TL. Bitter herbs: mainstream, magic and menace. Ann Intern Med. 1994;121:803-4. PubMed PMID: 7944058.

(Editorial accompanying Woolf [1994] regarding Jin Bu Huan Anodyne Tablets which were widely available before their withdrawal because of hepatotoxicity which was possibly caused by a contaminant).

Perharic L, Shaw D, Leon C, De Smet PA, Murray VS. Possible association of liver damage with the use of Chinese herbal medicine for skin disease. Vet Hum Toxicol. 1995;37:562-6. PubMed PMID: 8588298.

(9 reports of liver damage from a Chinese herbal medicine for skin conditions were made to London poisoning unit; 7 women and one man, ages 23 to 56 years, taking herbs for 2 weeks to 10 months [intermittently], 1 with fatal acute liver failure, 3 with jaundice [ALT usually very high with near normal Alk P], two had positive rechallenge; analysis showed 23 ingredients and 40 plant species, animal parts and a fungus).

Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine sho-saiko-to (xiao-chai-hu-tang). Dig Dis Sci. 1995;40:1845-8. PubMed PMID: 7648990.

(4 cases, 42 to 58 year old women, taking *Syo Saiko To* for 3-7 weeks, developed liver test elevations, 2 with jaundice, 2 with recurrence on restarting [peak ALT 135 to 1335 U/L], with resolution within 2 to 3 months of stopping).

Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs: possible toxic components. *Gut*. 1995;36:146–7. PubMed PMID: 7890220.

(Two patients, 39 and 61 year old women, developed jaundice 2 and 6 months after starting Chinese herbs for skin conditions [bilirubin 26 and 12.9 mg/dL, ALT 2440 and AST >1000 U/L, Alk P 261 and 311 U/L], resolving within 2-3 months of stopping, one had recurrence on restarting; analysis of products identified multiple plant species).

Vautier G, Spiller RC. Safety of complementary medicines should be monitored. *BMJ*. 1995;311:633. PubMed PMID: 7663283.

(32 year old man took Chinese herbal medication and 5 weeks later developed jaundice followed by acute liver failure and death; few details given, but product contained *Dictamnus dasycarpus*).

Centers for Disease Control and Prevention (CDC). Unexplained severe illness possibly associated with consumption of Kombucha tea--Iowa, 1995. *MMWR Morb Mortal Wkly Rep*. 1995;44(48):892–3, 899-900. PubMed PMID: 7476846.

(Two patients from a rural town in Iowa developed severe unexplained illness [lactic acidosis and cardiopulmonary collapse] after taking Kombucha tea for 2 months; cause was not identified).

Perron AD, Patterson JA, Yanofsky NN. Kombucha “mushroom” hepatotoxicity. *Ann Emerg Med*. 1995;26:660–1. PubMed PMID: 7486385.

(53 year old man developed fever, rash and abdominal cramping 4 weeks after starting and 2 weeks after stopping Kombucha tea [bilirubin normal, ALT 285 U/L, Alk P 168 U/L], resolving 1 month later).

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. PubMed PMID: 8774209.

(6 cases: 3 in children, 2 girls and 1 boy, ages 13, 19 and 30 months, with accidental ingestion of 5, 17 and 60 tablets of Jin Bu Huan presenting within hours with lethargy, ataxia, coma, respiratory depression, but with rapid recovery without sequelae; 3 cases in adults, 50, 55 and 70 year old women, becoming symptomatic 1, 2 and 24 weeks after starting Jin Bu Huan, 2 with marked ALT elevations but normal bilirubin, 1 with jaundice and ALT 1500 U/L, abnormalities persisting while herb was continued intermittently and falling to normal within 2 months of stopping).

Kaptchuk TJ. Acute hepatitis associated with Jin Bu Huan. *Ann Intern Med*. 1995;122:636. PubMed PMID: 7741903.

(Letter in response to Woolf [1994], arguing that the liver injury was not due to Jin Bu Huan, but rather another plant contaminant with high concentrations of the alkaloid, L-tetrahydropalmatine).

Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. *Am J Gastroenterol*. 1996;91:1436–8. PubMed PMID: 8678010.

(33 year old woman developed nausea within days of starting Ma Huang for weight loss followed at 3 weeks by jaundice [bilirubin 4.5 rising to 8 mg/dL, ALT 832 U/L, Alk P 178 U/L, ANA 1:160, asterixis], resolving within 4 weeks of stopping).

But PP, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from *Polygonum multiflorum*. *Vet Hum Toxicol*. 1996;38:280–2. PubMed PMID: 8829347.

(31 year old woman from Hong Kong developed jaundice several weeks after starting Shou Wu Pian for hair loss [bilirubin 4.0 rising to 6.1 mg/dL, ALT 870 U/L, Alk P 108 U/L], resolving within 3 weeks of stopping).

- De Smet PA, Van den Eertwegh AJ, Lesterhuis W, Stricker BH. Hepatotoxicity associated with herbal tablets. *BMJ*. 1996;313:92. PubMed PMID: 8688761.
- (69 year old woman developed jaundice six weeks after starting herbal tablets “Venencapsan” prepared locally from horse chestnut leaf, milfoil, celandine, sweet clover, milk thistle and dandelion root, recurring on reexposure [bilirubin 1.6 and 4.7 mg/dL, ALT 244 and 1004 U/L, Alk P 229 and 250 U/L], resolving rapidly on stopping).*
- Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. *J Clin Pharmacol*. 1997;37:344–50. PubMed PMID: 9115061.
- (Prospective analysis of 2609 samples of herbal medications in Taiwan found adulteration in 24%, major adulterants being caffeine, acetaminophen, nonsteroidal antiinflammatory agents, corticosteroids, antihistamines, salicylates, benzodiazepines and barbiturates).*
- 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. PubMed PMID: 9128330.
- (55 year old woman with chronic hepatitis developed jaundice one month after starting Dai Saiko To [bilirubin 11.2 mg/dL, ALT 390 U/L, ANA 1:2560], responding rapidly to prednisone therapy).*
- Matsuda R, Takahashi D, Chiba E, Kawana I, Tomiyama M, Ebira H, Ikegami T, et al. Nihon Shokakibyō Gakkai Zasshi. 1997;94(11):787–91. [A case of drug induced hepatitis and interstitial pneumonia caused by a herbal drug, Dai-saiko-to]. Japanese. PubMed PMID: 9396337.
- (65 year old man developed dyspnea and interstitial pneumonitis with abnormal liver tests 4 weeks after starting Dai Saiko To for autoimmune dermatitis, stopping at 6 weeks [bilirubin 1.2 mg/dL, ALT 675 U/L, Alk P 1070 U/L], resolving within a month of stopping).*
- Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study(1991-1995). *Drug Saf*. 1997;17:342–56. PubMed PMID: 9391777.
- (Five year experience of a Medical Toxicology Unit in London including 1297 enquiries including 37 for liver injury; 9 cases described, 5 due to valerian).*
- Levi M, Guchelaar HJ, Woerdenbag HJ, Zhu YP. Acute hepatitis in a patient using a Chinese herbal tea—a case report. *Pharm World Sci*. 1998;20:43–4. PubMed PMID: 9536471.
- (49 year old man developed jaundice 2 weeks after starting an herbal mixture for eczema [bilirubin 2.9 mg/dL, ALT 716 U/L, Alk P 78 U/L], with near normal values 3 months after stopping).*
- Picciotto A, Campo N, Brizzolara R, Giusto R, Guido G, et al. Chronic hepatitis induced by jin bu huan. *J Hepatol*. 1998;28:165–7. PubMed PMID: 9537855.
- (49 year old man found to have raised serum enzymes while taking Jin Bu Huan unbeknownst to his physicians [bilirubin 0.8 mg/dL, ALT 274 U/L, Alk P normal], which persisted for 10 months, biopsy showing chronic hepatitis and bridging fibrosis, liver tests falling to normal upon stopping herbal).*
- 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. PubMed PMID: 10230761.
- (28 year old developed jaundice after taking skullcap and Pau d’arco for 6 months for his multiple sclerosis [bilirubin 29.0 mg/dL, ALT 3917 U/L, Alk P 106 U/L, protime 20 seconds, ANA 1:640], progressing to liver failure and liver transplant 5 weeks later, dying shortly thereafter; explant showed sinusoidal obstruction syndrome).*
- Melchart D, Linde K, Hager S, Kaesmayr J, Shaw D, Bauer R, Weidenhammer W. Monitoring of liver enzymes in patients treated with traditional Chinese drugs. *Complement Ther Med*. 1999;7:208–16. PubMed PMID: 10709303.

- (Among 1450 patients with laboratory test results at the beginning and end of a hospital admission who were receiving traditional Chinese medicines, 3.1% had de novo abnormality of ALT, 1% with greater than two fold elevation, but other causes were likely in most cases).
- 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. PubMed PMID: 10404907.
- (Among 1507 patients treated with traditional Chinese herbs who had laboratory test results at the beginning and end of a hospital admission, 14 [0.9%] had greater than two fold elevation in ALT, 2 with symptoms, but other causes were likely in most cases).
- Brinkhaus B, Lindner M, Schuppan D, Hahn EG. Chemical, pharmacological and clinical profile of the East Asian medical plant *Centella asiatica*. *Phytomedicine*. 2000;7:427–48. PubMed PMID: 11081995.
- (*Centella asiatica* is an ancient medicinal herb, native to China and Southeast Asia, which contains pentacyclic triterpene derivatives and has been used for venous insufficiency and wound healing and as a sedative, analgesic, antidepressive, antimicrobial and immunomodulatory agent; toxicity includes allergic reactions and mild gastrointestinal upset).
- Brent J. Three new herbal hepatotoxic syndromes. *J Toxicol Clin Toxicol*. 1999;37:715–9. PubMed PMID: 10584584.
- (Summary of literature on hepatotoxicity of 3 herbals recently described including germander, Jin Bu Huan and chaparral).
- 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. PubMed PMID: 11151906.
- (48 year old man developed jaundice 3 days after starting Cascara sagrada [bilirubin 11.8 mg/dL, ALT 999 U/L, Alk P 309 U/L, ANA 1: 640], developing ascites, but recovering in 3 months).
- Shimizu I. Sho-saiko-to: Japanese herbal medicine for protection against hepatic fibrosis and carcinoma. *J Gastroenterol Hepatol*. 2000;15 Suppl:D84–90. PubMed PMID: 10759225.
- (Review of composition, clinical efficacy and mechanism of action of Sho Saiko To; contains 7 herbs, including *Bupleurum* root, *Pinellia tuber*, *Scutellaria* root and *Glycyrrhiza* root; active components likely to be saikosaponins and the antioxidants, baicalin and baicalein, which resemble silybinin).
- Stickel F, Seitz HK, Hahn EG, Schuppan D. *Z Gastroenterol*. 2001;39:225–32, 234–7. [Liver toxicity of drugs of plant origin]. German. PubMed PMID: 11324140.
- (Review of hepatotoxicity of botanicals including pyrrolizidine alkaloids, germander, celandine, chaparral, Chinese herbs and pennyroyal).
- Park GJH, 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. PubMed PMID: 11206309.
- (46 year old woman developed pruritus and jaundice 2 weeks after starting Shou Wu Pian [bilirubin 12.6 mg/dL, ALT 876 U/L, Alk P 185 U/L], resolving within a month of stopping).
- Stedman C. Herbal hepatotoxicity. *Semin Liver Dis*. 2002;22:195–206. PubMed PMID: 12016550.
- (Review and description of patterns of liver injury due to herbals, including discussion of potential risk factors, and herb-drug interactions).
- De Smet PAGM. Herbal remedies. *N Engl J Med*. 2002;347:2046–56. PubMed PMID: 12490687.

- (Review of status and difficulties of herbal medications including lack of standardization, federal regulation, contamination, safety, hepatotoxicity and drug-herb interactions; specific discussion of 4 herbs with therapeutic promise: ginkgo, hawthorn, saw palmetto and St. John's wort).*
- Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. *J Intern Med.* 2002;252:107–13. PubMed PMID: 12190885.
- (Systematic review of literature on adulteration of herbal products with conventional medications, in 15 case reports and 2 cases series of 21 patients; included NSAIDs, corticosteroids, benzodiazepines, diuretics and antidiabetic medications, in up to 24% of products).*
- Ingólfssdóttir K. Usnic acid. *Phytochemistry.* 2002;61:729–36. PubMed PMID: 12453567.
- (Usnic acid is a lichen metabolite used in creams, toothpaste, deodorants and as a preservative; also has antimicrobial activity and recently promoted as weight loss agent; it is toxic in high doses causing paralysis, ataxia and acidosis).*
- Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust.* 2002;177:440–3. PubMed PMID: 12381254.
- (6 cases of severe hepatitis in patients taking herbal medications including one on black cohosh alone and 5 taking multiple herbals including skullcap [n=3], valerian [n=2], chaparral [n=1] and greater celandine [n=1] for 1 to 14 weeks, presenting with jaundice [bilirubin 9.9-62.7 mg/dL, ALT 1293-3764 U/L, Alk P 80-219 U/L], the 1 on black cohosh alone requiring emergency liver transplantation, the other 5 resolving in 7-25 weeks, 3 treated with prednisone for prolonged cholestasis).*
- Divinsky M. Case report: jin bu huan – not so benign herbal medicine. *Can Fam Physician.* 2002;48:1640–2. PubMed PMID: 12449548.
- (45 year old woman developed jaundice while taking Jin Bu Huan for anxiety [bilirubin 2.4 mg/dL, ALT 1785 U/L, Alk P 115], with resolution in 6 weeks upon stopping herbal given to her by her visiting Chinese father).*
- Favreau JT, Ryu ML, Braunstein G, Orshansky G, Park SS, Coody GL, Love LA, Fong TL. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med.* 2002;136:590–5. PubMed PMID: 11955027.
- (7 patients, 4 women and 3 men, ages 20-32 years, developed symptoms and jaundice [n=5] or liver test abnormalities [n=2], 1-12 weeks after starting LipoKinetix [norephedrine, usnic acid, diiodothyronine, yohimbine, caffeine] for weight loss [peak bilirubin 2.2-14.6 mg/dL, ALT 438-14,150 U/L], resolving in 1 to 3 months of stopping).*
- 'Dietary supplement' warning. *FDA Consum.* 2002;36:4.
- (FDA warning letter concerning the toxicity of LipoKinetix, advising against its use).*
- Lewis JD, Strom BL. Balancing safety of dietary supplements with the free market. *Ann Intern Med.* 2002;136:616–8. PubMed PMID: 11955030.
- (Editorial on Favreau [2002] regarding LipoKinetix and the regulation of dietary supplements in the US).*
- McRae CA, Agarwal K, Mutimer D, Bassendine MF. Hepatitis associated with Chinese herbs. *Eur J Gastroenterol Hepatol.* 2002;14:559–62. PubMed PMID: 11984156.
- (Two patients; 31 year old woman developed jaundice 5 weeks after starting Chinese herbal root teas [bilirubin 8.2 rising to 32.0 mg/dL, ALT 2930 U/L] complicated by hemophagocytosis, but ultimate recovery over next 12 months; 32 year old man took 9 doses of Chinese herbal roots and developed diarrhea and then dark urine [bilirubin 37.8 mg/dL, ALT 242 U/L, INR 8.5], undergoing liver transplantation; explant showed massive necrosis).*

Haller CA, Dyer JE, Ko R, Olson KR. Making a diagnosis of herbal-related toxic hepatitis. *West J Med.* 2002;176:39–44. PubMed PMID: 11788538.

(42 year old woman took 3 herbals including Jin Bu Huan for insomnia and developed jaundice 10 weeks later [bilirubin 1.2 mg/dL, ALT 3386 U/L, Alk P 100 U/L], resolving in 6 weeks; 39 year old woman took several herbs including chaparral and developed jaundice and confusion [bilirubin 42.7 mg/dL, ALT 349 U/L], followed by liver failure and emergency liver transplantation).

De Smet PAGM. Herbal remedies. *N Engl J Med.* 2002;347:2046–56. PubMed PMID: 12490687.

(Review of status and problems with herbal medications, including lack of standardization and federal regulation, contamination, safety, hepatotoxicity and drug-herb interactions; specific discussion of 4 herbs with therapeutic promise: ginkgo, hawthorn, saw palmetto and St. John's wort).

Lin TJ, Tsai MS, Chiou NM, Deng JF, Chiu NY. Hepatotoxicity caused by *Breynia officinalis*. *Vet Hum Toxicol.* 2002;44:87–8. PubMed PMID: 11931510.

(Two women ages 43 and 51 years took large amounts of Breynia [one in suicide attempt] and rapidly developed vertigo, vomiting, headache and numbness [peak bilirubin 2.2 and 1.0 mg/dL, ALT 2443 and 2730 U/L, Alk P 103 and 107 U/L], resolving over the next 4 to 6 weeks).

Lin TJ, Su CC, Lan CK, Jiang DD, Tsai JL, Tsai MS. Acute poisonings with *Breynia officinalis*—an outbreak of hepatotoxicity. *J Toxicol Clin Toxicol.* 2003;41:591–4. PubMed PMID: 14514003.

(Breynia officinalis is used in many Chinese medicines, but is also a poison and can be mistaken for other herbs; 19 Chinese villagers drank a soup made from Breynia and developed diarrhea, nausea and liver test abnormalities [peak bilirubin 1.5-2.6 mg/dL, ALT 65-7398 U/L, Alk P 269 U/L], returning to normal in 1-2 months).

Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, Yoshioka M, Ishii H. Hepatic injury in 12 patients taking the herbal weight loss aids Chaso or Onshido. *Ann Intern Med.* 2003;139:488–92. PubMed PMID: 13679326.

(12 patients; 10 women and 2 men, ages 25-63 year, developed liver injury 1 to 6 weeks after starting weight loss aids [6 Chaso cases had bilirubin 0.6-19.8 mg/dL, ALT 283-4074 U/L, Alk P 185-768 U/L, 1 liver failure] [6 Onshido cases had bilirubin 0.6-24.2 mg/dL, ALT 634-4868 U/L, Alk P 255-867 U/L], resolving within 2 weeks to 6 months of stopping).

Schiano TD. Hepatotoxicity and complementary and alternative medicines. *Clin Liver Dis.* 2003;7:453–73. PubMed PMID: 12879994.

(Comprehensive review of herbal associated hepatotoxicity, including common patterns of presentation with discussion of Chinese herbal medicines, including Jin Bu Huan, Ma Huang, Shou Wu Pian, and Sho Saiko To).

Pittler MH, Ernest E. Systematic review: hepatotoxic events associated with herbal medicinal products. *Aliment Pharmacol Ther.* 2003;18:451–71. PubMed PMID: 12950418.

(Systematic review of published cases of hepatotoxicity due to herbal medications, listing 52 case reports or case series, most common agents being celandine [3], chaparral [3], germander [8], Jin Bu Huan [3], kava [1], Ma Huang [3], pennyroyal [1], skullcap [2], Chinese herbs [9] and valerian [1]).

Bajaj J, Knox JF, Komorowski R, Saeian K. The irony of herbal hepatitis: Ma-Huang-induced hepatotoxicity associated with compound heterozygosity for hereditary hemochromatosis. *Dig Dis Sci.* 2003;48:1925–8. PubMed PMID: 14627335.

(44 year old man developed jaundice 4 months after starting Hydroxycut with Ma Huang [bilirubin 3.5 mg/dL, ALT 3600 U/L], resolving in 1 month upon stopping; HFE testing revealed compound heterozygosity: C282Y/H63D).

- Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff SL. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg*. 2003;138:852–8. PubMed PMID: 12912743.
- (Among 20 patients undergoing liver transplantation for acute liver failure during 2001–2, 10 were attributed to herbal use: 3 Ma Huang, 3 kava, 2 LipoKinetix, 1 chaparral, 1 skullcap and 2 miscellaneous Chinese herbs).*
- 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. PubMed PMID: 15390328.
- (Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, including 7 [5%] cases attributed to herbal medications).*
- Durazo FA, Lassman C, Han SH, Saab S, Lee NP, Kawano M, Saggi B, et al. Fulminant liver failure due to usnic acid for weight loss. *Am J Gastroenterol*. 2004;99:950–2. PubMed PMID: 15128366.
- (28 year old woman developed nausea and fatigue 2 weeks after starting usnic acid and, despite stopping it, developed jaundice, confusion and hepatic failure requiring liver transplantation [bilirubin 28 mg/dL, ALT 449 U/L, AST 1016 U/L, INR 4.6]; the explant demonstrated massive necrosis).*
- Willett KL, Roth RA, Walker L. Workshop overview: Hepatotoxicity assessment for botanical dietary supplements. *Toxicol Sci*. 2004;79:4–9. PubMed PMID: 14976355.
- (Summary of a workshop on the hepatotoxicity of botanicals focusing upon mechanisms of hepatic injury and means of prediction and prevention).*
- Han D, Matsumaru K, Tettori D, Kaplowitz N. Usnic acid-induced necrosis of cultured mouse hepatocytes: inhibition of mitochondrial function and oxidative stress. *Biochem Pharmacol*. 2004;67:439–51. PubMed PMID: 15037196.
- (Usnic acid caused necrosis of isolated mouse hepatocytes, probably by uncoupling of electron transport in mitochondria, oxidative stress and depletion of glutathione).*
- Myers SP, Cheras PA. The other side of the coin: safety of complementary and alternative medicine. *Med J Aust*. 2004;181:222–5. PubMed PMID: 15310261.
- (Discussion of the safety of complementary and alternative medicines).*
- Mazzanti G, Battinelli L, Daniele C, Mastroianni CM, Lichtner M, Coletta S, Costantini S. 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. PubMed PMID: 15069011.
- (78 year old man developed jaundice 1 month after starting Shou Wu Pian for chronic prostatitis [bilirubin 25.5 mg/dL, ALT 1276 U/L, Alk P 409 U/L], resolving rapidly upon stopping).*
- Sonmez A, Yilmaz MI, Mas R, Ozcan A, Celasun B, Dogru T, Taslipinar A, Kocar IH. Subacute cholestatic hepatitis likely related to the use of senna for chronic constipation. *Acta Gastroenterol Belg*. 2005;68:385–7. PubMed PMID: 16268429.
- (77 year old male developed jaundice after taking a senna preparation for constipation for 3 months [bilirubin 4.9 rising to 16.9 mg/dL, ALT 657 U/L, Alk P 160 U/L], resolving within 1 month of stopping the herbal).*
- Hsu LM, Huang YS, Chang FY, Lee SD. ‘Fat burner’ herb, usnic acid, induced acute hepatitis in a family. *J Gastroenterol Hepatol*. 2005;20:1138–9. PubMed PMID: 15955234.
- (3 sisters with toxicity from herbal “fat burner” consisting of soybean and usnic acid; 36 year old woman had abdominal pain 2 weeks after starting herbal [bilirubin normal, ALT 442 U/L, Alk P 217 U/L], resolving within 6 weeks; 32 year old sister developed jaundice after 4 weeks of use [bilirubin 29 mg/dL, ALT 778 U/L, Alk P 118 U/L, INR 2.6], resolving in 4 months; third sister stopped the herbal after 3 days because of fatigue).*

- Nam SW, Baek JT, Lee DS, Kang SB, Ahn BM, Chung KW. A case of acute cholestatic hepatitis associated with the seeds of *Psoralea corylifolia* (Boh-Gol-Zhee). *Clin Toxicol (Phila)*. 2005;43:589–91. PubMed PMID: 16255343.
- (44 year old woman developed nausea followed by jaundice 7 weeks after starting daily ingestion of Psoralea corylifolia tea [bilirubin 7.3 mg/dL, ALT 398 U/L, Alk P 367 U/L], with rapid resolution on stopping).*
- Panis B, Wong DR, Hooymans PM, De Smet PAMG, Rosias PPR. Recurrent toxic hepatitis in a Caucasian girl related to the use of Shou-Wu-Pian, a Chinese herbal preparation. *J Pediatr Gastroenterol Nutr*. 2005;41:256–8. PubMed PMID: 16056110.
- (5 year old girl developed jaundice 4 months after being started on Shou Wu Pian [bilirubin 4.9 mg/dL, ALT 1543 U/L, Alk P normal], resolving within 5 weeks and recurring within 4 weeks of restarting, with slower recovery [5 months]).*
- Casallo Blanco S, Blanco González J, Marcos Sánchez F, Alvarez Cercadillo R, Moreno Palomares M. Hepatitis tóxica secundaria a hierbas chinas. *Gastroenterol Hepatol*. 2005;28(5):307–8. [Toxic hepatitis induced by Chinese herbs]. Spanish. PubMed PMID: 15871817.
- (32 year old man developed jaundice a few weeks after starting an unknown Chinese herbal medication [bilirubin 24.5 mg/dL, ALT 2650 U/L, GGT 73 U/L], resolving within 8 weeks of stopping).*
- López-Briz E, Garrigues-Gil V. Hepatitis por hierbas chinas. *Gastroenterol Hepatol*. 2005;28(10):656. [Hepatitis due to Chinese herbs]. Spanish. PubMed PMID: 16373019.
- (Letter in response to Cassalo Blanco [2005] discussing the possible toxic agent in the Chinese herbal preparation).*
- Arneborn P, Jansson A, Böttiger Y. *Lakartidningen*. 2005;102:2071–2. [Acute hepatitis in a woman after intake of slimming pills bought via Internet]. Swedish. PubMed PMID: 16097177.
- (20 year old overweight woman developed nausea followed by jaundice 4 weeks after starting a weight loss agent [Termoxical, containing usnic acid] purchased over the Internet [bilirubin 4.9 mg/dL, ALT 1320 U/L, Alk P 198 U/L], resolving within a month of stopping).*
- 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. PubMed PMID: 16570576.
- (52 year old woman developed jaundice 1.5 months after starting Xiao Chai Hu Tang, known in Japan as Syo Saiko To [bilirubin 1.9 mg/dL, ALT 2028 U/L, Alk P 213 U/L], resolving within 2 months of stopping).*
- Yuen MF, Tam S, Fung J, Wong DK, Wong BC, Lai CL. Traditional Chinese medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. *Aliment Pharmacol Ther*. 2006;24:1179–86. PubMed PMID: 17014576.
- (Among 45 patients with chronic hepatitis B hospitalized because of liver dysfunction at Queen Mary Hospital, Hong Kong during 2004, 7 appeared to have liver injury caused by traditional Chinese herbal medications, marked by worsening of liver tests, lack of IgM anti-HBc and low or no detectable HBV DNA; two died and two underwent liver transplantation).*
- Cárdenas A, Restrepo JC, Sierra F, Correa G. Acute hepatitis due to shen-min: a herbal product derived from *Polygonum multiflorum*. *J Clin Gastroenterol*. 2006;40(7):629–32. PubMed PMID: 16917407.
- (28 year old woman developed fatigue followed by jaundice 8 weeks after starting Shen Min for hair loss [bilirubin 12.3 mg/dL, ALT 2922 U/L, Alk P 153 U/L], resolving within 4 weeks of stopping the herbal).*
- 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. PubMed PMID: 16610575.

(Two cases: 38 year old woman developed jaundice 3 months after starting 1350 mg daily of UCP-1 [bilirubin 23.0 mg/dL, ALT 1636 U/L, Alk P 195 U/L, protime 22.7 sec], progressing to hepatic failure and successful liver transplantation; 38 year old husband of previous case developed back pain 3 months after starting UCP-1 [bilirubin 0.6 mg/dL, ALT 1462 U/L], with rapid resolution on stopping and normal values 4 months later: Case 1 usnic acid).

Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, Lim SG. Drug-induced liver injury at an Asian center: a prospective study. *Liver Int.* 2007;27:465–74. PubMed PMID: 17403186.

(Prospective survey of drug induced liver injury presenting over 26 months at a single hospital in Singapore identified 31 cases, ages 18-90 years, 55% male, Chinese traditional medicines being implicated in 17 [55%] and Malay agents in 5 cases [16%]; adulterants were found in 9 of 31 tested traditional agents [codeine, corticosteroids, metformin, mercury, nonsteroidal antiinflammatory agents]).

Seeff LB. Herbal hepatotoxicity. *Clin Liver Dis.* 2007;11:577–96. PubMed PMID: 17723921.

(Review of herbal-induced hepatotoxicity, with a review of Chinese herbal medicines such as Chaso, Onshido, Sho Saiko To, Jin Bu Huan, Ma Huang and Shou Wu Pian).

Chitturi S, Farrell GC. Hepatotoxic slimming aids and other herbal hepatotoxins. *J Gastroenterol Hepatol.* 2008;23:366–73. PubMed PMID: 18318821.

(Review of hepatotoxicity of herbal medications focusing upon those used for weight loss including nitrosofenfluramine, usnic acid, ephedra, germander, skullcap and green tea).

Foti RS, Dickmann LJ, Davis JA, Greene RJ, Hill JJ, Howard ML, Pearson JT, et al. Metabolism and related human risk factors for hepatic damage by usnic acid containing nutritional supplements. *Xenobiotica.* 2008;38:264–80. PubMed PMID: 18274956.

(In vitro analyses of usnic acid and cytochrome P450 enzymes found that it was a potent inhibitor of CYP 2C19 and 2C9, suggesting that it may cause significant drug-herb interactions).

Laird AR, Ramchandani N, deGoma EM, Avula B, Khan IA, Gesundheit N. Acute hepatitis associated with the use of an herbal supplement (*Polygonum multiflorum*) mimicking iron-overload syndrome. *J Clin Gastroenterol.* 2008;42:861–2. PubMed PMID: 18580499.

*(35 year old man developed jaundice “several months” after starting “NuHair” [containing *Polygonum multiflorum*] for hair loss [bilirubin 4.6 rising to 13.7 mg/dL, ALT 2714 U/L, Alk P 137 U/L, INR 1.3], resolving 4 months after stopping).*

García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Liver injury induced by “natural remedies”: an analysis of cases submitted to the Spanish Liver Toxicity Registry. *Rev Esp Enferm Dig.* 2008;100:688–95. PubMed PMID: 19159172.

*(Among 521 cases of drug induced liver injury submitted to a Spanish registry, 13 [2%] were due to herbals, including *Camellia sinensis* [green tea], *Cassia angustifolia* [senna], kava, valerian, *Rhamnus purshianus* [cascara], fitosoja [soy plant], biosoja [soy extract], *Aesculus hippocatanum* [horse chestnut], chitosan [deacetylated chitin] and *Couterea latifloral* [Copalchi]).*

Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology.* 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 9% of cases were attributed to herbals and dietary supplements).

Guo L, Shi Q, Fang JL, Mei N, Ali AA, Lewis SM, Leakey JE, Frankos VH. Review of usnic acid and *Usnea barbata* toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2008;26:317–38. PubMed PMID: 19034791.

(Usnea extract has been used in traditional Chinese medicine for centuries as an antimicrobial and for other uses, including in cosmetics, food, toothpaste and mouthwash; in vitro, it has mitochondrial uncoupling properties and was therefore used for weight loss; FDA received 21 adverse event reports including 1 death attributed to dietary supplements containing usnic acid [LipoKinetix and UCP-1] and 12 cases were described in the literature, leading to warnings and recommendations for it to be withdrawn).

Navarro VJ. Herbal and dietary supplement hepatotoxicity. *Semin Liver Dis.* 2009;29:373–82. PubMed PMID: 19826971.

(Overview of the regulatory environment, clinical patterns, and future directions in research with HDS including traditional Chinese herbal medicines and usnic acid).

Cheung WI, Tse ML, Ngan T, Lin J, Lee WSK, Poon WT, Mak TWL, et al. Liver injury associated with the use of *Fructus Psoraleae* (Bol-gol-zhee or Bu-gu-zhi) and its related proprietary medicine. *Clin Toxicol (Phila).* 2009;47:683–5. PubMed PMID: 19640237.

(3 cases of liver injury from dried seeds of P. corylifolia used to treat skin conditions, 2 men and 1 woman, 20-39 years old, taking product for 2-8 weeks, developed jaundice [bilirubin 5.1-5.5 mg/dL, ALT 720-2248 U/L, Alk P 115-177 U/L, INR 1.1-1.2], resolving within 4-9 weeks of stopping; analysis of product revealed psoralen, isopsoralen and coumestrol).

Jacobsen C, Semb S, Kromann-Andersen H. *Ugeskr Laeger.* 2009;171:3367–9. [Toxic hepatitis following consumption of the herbal medicinal product *Cascara Sagrada*]. Danish. PubMed PMID: 19925744.

(49 year old developed jaundice 4 weeks after starting daily ingestion of Cascara sagrada for constipation [bilirubin 8.4 rising to 24.6 mg/dL, ALT 944 U/L, ascites], resolving in 4 months).

Wang YP, Shi B, Chen YX, Su J, Jiang CF, Xie WF. Drug-induced liver disease: an 8 year study of patients from one gastroenterological department. *J Dig Dis.* 2009;10:195–200. PubMed PMID: 19659787.

(30 patients with drug induced liver disease seen at a single medical university in Shanghai between 2000 and 2008, of which 12 were attributed to Chinese herbs, but specific agents not discussed, 9 were jaundiced, 6 had hepatocellular, 3 cholestatic and 2 mixed patterns of injury).

Jacobsson I, Jönsson AK, Gerdén B, Hägg S. Spontaneously reported adverse reactions in association with complementary and alternative medicine substances in Sweden. *Pharmacoepidemiol Drug Saf.* 2009;18:1039–47. PubMed PMID: 19650152.

(Review of 778 spontaneous reports of adverse reactions to herbals to a Swedish Registry found multiple agents associated with liver injury including purple cornflower, black cohosh, shark liver oil, valerian, horsetail, ginseng, green tea, ginkgo and aloe vera).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology.* 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury of which 12 [9%] were due to herbals including usnic acid [2], thermoslim [1], Ma Huang [1], horny goat weed [1], black cohosh [1], hydroxycut [1] and unspecified herbals [4]).

Furukawa M, Kasajima S, Nakamura Y, Shouzushima M, Nagatani N, Takinishi A, Taguchi A, et al. Toxic hepatitis induced by show-wu-pian, a Chinese herbal preparation. *Intern Med.* 2010;49(15):1537–40. PubMed PMID: 20686286.

(53 year old Japanese woman developed fatigue after taking Shou Wu Pian for 8 months [bilirubin 1.2 mg/dL, ALT 417 U/L, Alk P 1425 U/L, ANA 1:320], resolving within 2 months of stopping).

Bae SH, Kim DH, Bae YS, Lee KJ, Kim DW, Yoon JB, Hong JH, Kim SH. Korean J Hepatol. 2010;16:182–6. [Toxic hepatitis associated with Polygoni multiflori]. PubMed PMID: 20606503.

(54 year old Korean woman developed fatigue 1 month after starting Shou Wu [ALT 1136 U/L, Alk P 324 U/L], resolving rapidly but recurring upon restarting).

Chou SL, Chou MY, Kao WF, Yen DH, Yen LY, Huang CI, Lee CH. Bajiaolian poisoning—a poisoning with high misdiagnostic rate. Am J Emerg Med. 2010;28:85–9. PubMed PMID: 20006208.

(Review of records of 4 poison centers in Taiwan from 1985 to 2003 identified 17 cases of Ba Jiao Lian toxicity, 15 were initially misdiagnosed; presenting with nausea, weakness, confusion, gastrointestinal bleeding, and abnormal liver tests followed by sensory-motor and autonomic neuropathy).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, among the 41 most commonly implicated agents, none were herbals or dietary supplements).

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. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, four cases were attributed to Ayurvedic medications).

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(7): 750, 258e-62e.

(Two patients developed liver injury within weeks of starting “Move Free Advanced” which contains Chinese skullcap [Scutellaria baicalensis] for arthralgias, resolving upon stopping).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N. Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J Pediatr Gastroenterol Nutr. 2011;53:182–9. PubMed PMID: 21788760.

(Among 30 children with suspected drug induced liver injury, only one case was attributed to an herbal; hydroxycut).

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int. 2011;31:595–605. PubMed PMID: 21457433.

(Review of current understanding of liver injury from herbals and dietary supplements focusing upon Herbalife and Hydroxycut products, green tea, usnic acid, Noni juice, Chinese herbs, vitamin A and anabolic steroids).

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32:1543–56. PubMed PMID: 22928722.

(A systematic compilation of all publications on the hepatotoxicity of specific herbals identified 185 publications on 60 different herbs, including one case report attributed to saw palmetto [Lapi 2010]).

Jiménez-Encarnación E, Ríos G, Muñoz-Mirabal A, Vilá LM. Euforia-induced acute hepatitis in a patient with scleroderma. BMJ Case Rep. 2012;2012:bcr2012006907. PubMed PMID: 23257938.

- (45 year old woman developed jaundice 1 month after starting Euphoria, an herbal mixture whose ingredients included aloe vera, resveratrol, green tea, noni juice and multiple berries [bilirubin 17.7 mg/dL, ALT 837 U/L, Alk P 134 U/L], with slow recovery after stopping).*
- Weinstein DH, Twaddell WS, Raufman JP, Philosophe B, Mindikoglu AL. SlimQuick™ - associated hepatotoxicity in a woman with alpha-1 antitrypsin heterozygosity. *World J Hepatol.* 2012;4:154–7. PubMed PMID: 22567188.
- (24 year old woman training for a marathon developed jaundice 4 months after starting SlimQuick [bilirubin 4.0 mg/dL, ALT 2615 U/L, Alk P 200 U/L], was treated with prednisone and had a prompt improvement and was later able to stop corticosteroids without relapse).*
- Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther.* 2013;37:3–17. PubMed PMID: 23121117.
- (Review of HDS associated hepatotoxicity with specific discussion of Ayurvedic, Chinese and Kampo herbal products such as Jin Bu Huan, Ma Huang, Dai-saiko-to).*
- García Cortés M, Fernández Castañer A. *Rev Esp Enferm Dig.* 2013;105:433. [Hepatotoxicity by herbal products]. Spanish. PubMed PMID: 24206556.
- (Information for patients on the hepatotoxicity of herbal medications mentioning the list of botanicals that are prohibited in Spain).*
- Navarro VJ, Seeff LB. Liver injury induced by herbal complementary and alternative medicine. *Clin Liver Dis.* 2013;17:715–35. PubMed PMID: 24099027.
- (Review of herbal hepatotoxicity including discussion of Chinese herbals and traditional remedies).*
- Abdualmjid RJ, Sergi C. Hepatotoxic botanicals - an evidence-based systematic review. *J Pharm Pharm Sci.* 2013;16(3):376–404. PubMed PMID: 24021288.
- (Extensive review of the hepatotoxicity of botanicals).*
- Patel SS, Beer S, Kearney DL, Phillips G, Carter BA. Green tea extract: a potential cause of acute liver failure. *World J Gastroenterol.* 2013;19:5174–7. PubMed PMID: 23964154.
- (16 year old boy developed jaundice 8 weeks after starting a green tea extract for weight loss [bilirubin 14.8 mg/dL, ALT 2984 U/L, Alk P 186 U/L, INR 1.3] with severe course, but ultimate resolution within 6 months).*
- Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. *World J Hepatol.* 2014;6:17–32. PubMed PMID: 24653791.
- (Review of value and relative reliability of RUCAM system of adjudication of causality in drug and herbal induced liver injury).*
- Dong H, Slain D, Cheng J, Ma W, Liang W. Eighteen cases of liver injury following ingestion of *Polygonum multiflorum*. *Complement Ther Med.* 2014;22:70–4. PubMed PMID: 24559819.
- (Between 2005 and 2012, 18 patients with suspected Fo ti [Polygonum multiflorum] hepatotoxicity were seen at a referral hospital in China, ages 19-63 years, 19 men, 10 women, onset after 1 to 120 days [bilirubin 0.6-16.8 mg/dL, ALT 601-4095 U/L, Alk P 89-816 U/L], 12 with jaundice, all hepatocellular, all recovered).*
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(56 year old woman with glioblastoma developed liver injury 32 days after starting temozolomide [bilirubin 16.7 mg/dL, ALT 585 U/L, Alk P not given] having also taken a Chinese herbal formula known as Bu Zhong Yi Qi Wan for 2 weeks; after recovery, she was able to restart temozolomide without recurrence of liver injury).
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*(Among 69 children with drug induced liver injury identified between 2009 and 2012, Western medications accounted for 57% [antibiotics in most] and Chinese patent medicine or decoctions for only 22% [Ephedra, *Polygonum*, and others]).*
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(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 145 [16%] were attributed to herbal and dietary supplements of which 5 were referred to as Chinese and 3 as Korean herbs or herbal products).

Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. *Gastroenterology*. 2015;148:517–532.e3. PubMed PMID: 25500423.

(Extensive review of herbal associated liver injury).

Frenzel C, Teschke R. Herbal hepatotoxicity: clinical characteristics and listing compilation. *Int J Mol Sci*. 2016;17:E588. pii. PubMed PMID: 27128912.

(Review of the challenges in the diagnosis of hepatotoxicity due to herbal products including problems of misidentifications, adulterants, impurities, range of clinical presentations, lack of diagnostic markers, and alternative diagnoses; an extensive compilation of herbs reported to have caused liver injury).

Zhang P, Ye Y, Yang X, Jiao Y. Systematic review on Chinese herbal medicine induced liver injury. *Evid Based Complement Alternat Med*. 2016;2016:3560812. PubMed PMID: 27651817.

(Systematic review of the literature on liver injury due to traditional Chinese herbal medicines found 17 articles and 114 cases from China, Korea, Japan and the US, but only 54 were judged at least probable with average latency of 30 days, mean ALT 1246 U/L, Alk P 225, bilirubin not given; 81% hepatocellular, 1 fatal and 1 requiring liver transplantation, most frequently implicated agent being He Shou Wu [n=65]).

Teschke R, Larrey D, Melchart D, Danan G. Traditional Chinese Medicine (TCM) and herbal hepatotoxicity: RUCAM and the role of novel diagnostic biomarkers such as MicroRNAs. *Medicines (Basel)*. 2016;3:18. PubMed PMID: 28930128.

(Review of the challenges in assessing causality in cases of liver injury in patients on traditional Chinese medicines and role of the RUCAM in standardization of assessment and use of new biomarkers).

Zhang P, Ye Y, Yang X, Jiao Y. Systematic review on Chinese herbal medicine induced liver injury. *Evid Based Complement Alternat Med*. 2016;2016:3560812. PubMed PMID: 27651817.

(Systematic review of the literature on hepatotoxicity of traditional Chinese medicines identified 17 relevant publications with a total of 114 cases; 83 from China, 26 Korea, 4 US and 1 Japan; 4 single herbs, 21 patent medicines and 4 decoctions; mostly frequently implicated agent being He Shou Wu [65]).

Melchart D, Hager S, Dai J, Weidenhammer W. Quality control and complication screening programme of Chinese medicinal drugs at the First German Hospital of Traditional Chinese Medicine - a retrospective analysis. *Forsch Komplementmed*. 2016;23 Suppl 2:21–8. PubMed PMID: 27272353.

(Among 994 patients treated with Chinese herbal medications, 6 developed elevations in serum ALT [31-361 U/L] or AST [39-326 U/L], but other reasons for the elevations were found in most).

Melchart D, Hager S, Albrecht S, Dai J, Weidenhammer W, Teschke R. Herbal Traditional Chinese Medicine and suspected liver injury: a prospective study. *World J Hepatol*. 2017;9:1141–1157. PubMed PMID: 29085558.

(Among 21,470 patients admitted to a German hospital for Traditional Chinese Medicine between 1994 and 2015, 870 developed elevations in ALT levels during the admission, but only 26 were greater than 5 times ULN, of whom only 8 were consider probably due to herbal medicine).

Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. *Food Chem Toxicol*. 2017;107:472–501. PubMed PMID: 27402097.

(Description of an online compendium of cases of liver toxicity attributed to HDS products).

Jing J, Teschke R. Traditional Chinese Medicine and herb-induced liver injury: comparison with drug-induced liver injury. *J Clin Transl Hepatol*. 2018;6:57–68. PubMed PMID: 29577033.

(Comparison of general clinical features of cases of drug induced vs herbal and dietary supplement induced liver injury in the published literature suggested that injury of herbal products was more likely to be hepatocellular and was overall less severe than cases from conventional medications).

Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A, Cabello MR, Robles-Diaz M, Sanabria-Cabrera J, Sanjuan-Jimenez R, et al; Spanish DILI Registry. Herbal and dietary supplement-induced liver injuries in the Spanish DILI Registry. *Clin Gastroenterol Hepatol.* 2018;16:1495–1502. PubMed PMID: 29307848.

(Among 856 cases of hepatotoxicity enrolled in the Spanish DILI Registry between 1994 and 2016, 32 were attributed to herbal products, the most frequent cause being Green tea [n=8] and Herbalife products [n=6], while none were attributed to Aloe vera).

Liu Z, He X, Wang L, Zhang Y, Hai Y, Gao R. Chinese herbal medicine hepatotoxicity: the evaluation and recognition based on large-scale evidence database. *Curr Drug Metab.* 2019;20:138–146. PubMed PMID: 30101702.

(Review of the challenges of establishing causality in cases of suspected drug induced liver injury from Traditional Chinese Medicine).

Li A, Gao M, Zhao N, Li P, Zhu J, Li W. Acute liver failure associated with Fructus Psoraleae: a case report and literature review. *BMC Complement Altern Med.* 2019;19:84. PubMed PMID: 30975110.

(53 year old woman developed jaundice 7 months after starting Qubaibabuqi tablets [a traditional Uyghur medicine] for vitiligo [bilirubin 1.6 mg/dL, ALT 804 U/L, Alk P not given], with rapid progression of liver failure and death within 4 days; the implicated ingredient being seeds of Psoraleae corylifolia which has been implicated in 6 non-fatal of acute hepatitis in the literature).

Chow HC, So TH, Choi HCW, Lam KO. Literature review of Traditional Chinese Medicine herbs-induced liver injury from an oncological perspective with RUCAM. *Integr Cancer Ther.* 2019;18:1534735419869479. PubMed PMID: 31405304.

(Systematic review of the literature on Tradition Chinese Medicine induced liver injury identified 50 publications and 194 causality confirmed cases including 80 due to Polygonum multiflorum [Fo Ti], 28 to Camellia sinensis [green tea], 7 to Dictamnus dasycarpus [Bai Xian Pi], 4 to Gynura segetum, 3 to Lycopodium serratum, 2 to Pueraria lobata and 1 to each of 14 others).

Ghorbani A, Zarvandi M, Rakhshandeh H. A randomized controlled trial of a herbal compound for improving metabolic parameters in diabetic patients with uncontrolled dyslipidemia. *Endocr Metab Immune Disord Drug Targets.* 2019;19:1075–1082. PubMed PMID: 30727929.

(Among 50 patients with diabetes and dyslipidemia treated with a multiingredient herbal supplement [with aloe vera, fenugreek, black seed, psyllium, garlic and milk thistle] or placebo twice daily for 12 weeks, cholesterol, triglycerides, and HgA1c levels improved, and there was “no unwarranted effect” on serum creatinine, ALT or AST).

Cai P, Qiu H, Qi F, Zhang X. The toxicity and safety of Traditional Chinese Medicines: Please treat with rationality. *Biosci Trends.* 2019;13:367–373. PubMed PMID: 31564696.

(Commentary on issue of hepatotoxicity of Traditional Chinese Medicine which can be avoided by use of appropriate dosing of agents for their intended use only, not given chronically as a “dietary supplement” and with appropriate monitoring and caution).

Liu Y, Zhan SP, Song L, Chen Y, Jia YT, Liu F, Sun FJ, Wang Q, Xia PY. Drug-induced liver injury: clinical and etiologic features at a large tertiary teaching hospital in China. *Med Sci Monit.* 2020;26:e919435. PubMed PMID: 32172275.

(Among 1811 patients with drug induced liver injury seen at a large referral hospital between 2011 and 2016, 462 [42%] were due to conventional medications, 391 [36%] to herbal products and 189 [17%] to both; 172 [16%] were due to antibiotics and 198 [18%] to Traditional Chinese Medicines).

Bessone F, García-Cortés M, Medina-Caliz I, Hernandez N, Parana R, Mendizabal M, Schinoni MI, et al. Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI Network. *Clin Gastroenterol Hepatol. Clin Gastroenterol Hepatol.* 2022;20(3):e548–e563. PubMed PMID: 33434654.

(Among 367 cases of hepatotoxicity enrolled in the Latin American DILI Network between 2011 and 2019, 29 [8%] were attributed to herbal products, the most frequent being Green tea [n=7], Herbalife products [n=5] and Garcinia [n=3]).

Ballotin VR, Bigarella LG, Brandão ABM, Balbinot RA, Balbinot SS, Soldera J. Herb-induced liver injury: Systematic review and meta-analysis. *World J Clin Cases.* 2021;9:5490–5513. PubMed PMID: 34307603.

(Systematic review of the literature on herb induced liver injury identified 446 references describing 936 cases due to 79 different herbal products, the most common being He Shou Wu [91, Fo ti or Polygonium multiflorum], Green tea [90], Herbalife products [64], Kava [62], Greater celandine [48], Germander [35], Skullcap [35], Kratom [33], Gynura segetum [29], Garcinia cambogia [29], Ma huang [27], Chaparral [26], Senna [25], Aloe vera [22], and Jin Bu Huan [Lycopodium serratum, 19]).