

Editorials

How Herbal Remedies affect Clinical Laboratory Test Results

Herbal medicines are readily available worldwide from stores without prescription. In the USA, the sale of herbal medicines increased from US\$ 200 million in 1988 to over US\$ 3.3 billion in 1997. The majority of the population who use herbal medicines in the USA has a college degree and is in the 25–49 years' age group. In one study, 65% of people thought that herbal medicines are safe.¹ In the USA, most herbal medicines are sold under the Dietary Supplement Health and Education Act of 1994 and are not regulated. A herbal medicine can affect laboratory test results by one of three mechanisms.

1. Direct assay interference, most commonly with immunoassays due to cross-reactivity of a component present in the preparation. For example, falsely elevated digoxin levels may be observed using the fluorescence polarization immunoassay (FPIA) for digoxin due to ingestion of the Chinese medicine *chan su*, *lu-shen-wan* or *dan shen*.
2. Physiological effects, either through toxicity or enzyme induction due to the use of herbal products. For example, *kava-kava* causes liver toxicity and elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels in healthy individuals.
3. A herbal product may contain undisclosed drugs or heavy metals.

Herbal remedies and interference with assays for therapeutic drug monitoring

Recently published reports indicate that only certain digoxin immunoassays are affected by herbal medicines. Chinese medicines such as *chan su*, *dan shen*, *ginseng* and oleander contain herbal products that interfere with various digoxin immunoassays. The Indian Ayurvedic medicine *ashwagandha* also demonstrates moderate interference with FPIA (Abbott Laboratories) for digoxin.²

The Chinese medicines *chan su* and *lu-shen-wan* contain bufalin which is structurally similar to digoxin. *Chan su* is very toxic and death of a woman has been reported after ingestion of Chinese herbal tea containing *chan su*.³ Panesar reported an apparent digoxin concentration of 1124 pmol/L (0.88 ng/ml) in healthy volunteers who ingested *lu-shen-wan* pills, which contain *chan su*.⁴ Ingestion of *chan su* and related drugs can also cause positive interference (falsely elevated serum digoxin levels) in serum digoxin measurement by FPIA and negative interference by the microparticle enzyme immunoassay (MEIA, Abbott Laboratories). Other digoxin immunoassays such as EMIT 2000, Synchron LX system (Beckman), Tina-quant (Roche Diagnostics) and turbidimetric (Bayer Diagnostics), which use monoclonal antibody against digoxin, are less affected by these Chinese medicines compared with FPIA and MEIA, which use polyclonal antibodies. The interfering components in *chan su* are very strongly bound to serum proteins and are absent in protein-free ultrafiltrates. In contrast, only 25% of digoxin is bound to serum protein and is present in the ultrafiltrate. Therefore, monitoring free digoxin concentration can minimize the interference of *chan su* in serum digoxin measurements.⁵

Dan shen is a Chinese medicine prepared from the root of *Salvia miltiorrhiza* and

has been in use in China for many centuries for the treatment of various cardiovascular diseases including angina pectoris. *Dan shen* causes modest interference with polyclonal-based digoxin immunoassays such as MEIA and FPIA. Chemiluminescent assay (Bayer), EMIT 2000 digoxin assay, Roche and Beckmann digoxin assays are free from interference by *dan shen*.⁶

The cardiac glycosides present in oleander cross-react with digoxin immunoassays. Osterloh *et al.* reported an apparent digoxin level of 5.8 ng/ml using the FPIA digoxin assay after suicidal ingestion of oleander tea in a patient with no history of taking any digoxin. The person eventually died from oleander toxicity.⁷ Eddleston *et al.* reported a mean apparent serum digoxin concentration of 1.49 nmol/L (1.16 ng/ml) in patients who were poisoned with oleander but eventually discharged from the hospital. Severe toxicity from oleander resulted in a mean apparent serum digoxin concentration of 2.83 nmol/L (2.21 ng/ml) as measured by the FPIA digoxin assay.⁸

Unexpectedly low levels of therapeutic drugs: Interaction of St John's wort with drugs

Unexpectedly low levels of a therapeutic drug in a patient who showed therapeutic levels before may have been due to initiation of self-therapy with St John's wort. St John's wort is an herbal antidepressant prepared from *Hypericum perforatum*, a perennial herb. CYP3A4 is the most abundant isoenzyme of cytochrome P450 and is responsible for the metabolism of more than 73 drugs and numerous endogenous compounds. The active components of St John's wort, especially hyperforin, induce CYP3A4 and CYP2B6 probably through activation of a nuclear steroid/pregnane and xenobiotic receptor.⁹ St John's wort also induces P-glycoprotein drug transporter and may reduce the efficacy of drugs where hepatic metabolism may not be the major pathway of clearance. The component hypericin may be the active ingredient that modulates P-glycoprotein.¹⁰

Self-medication with St John's wort may cause treatment failure due to significant reduction in plasma drug concentrations because of an increase in the clearance of drugs. Published reports indicate that St John's wort significantly reduces steady-state plasma concentrations of cyclosporin, tacrolimus, amitriptyline, digoxin, fexofenadine, indinavir, methadone, midazolam, nevirapine, phenprocoumon, saquinavir, simvastatin, theophylline and warfarin.^{11,12} Increased clearance of oral contraceptives has also been reported. Moreover, herbal products are not known to be prepared by using rigorous standards and concentrations of active ingredients may vary widely. St John's wort containing low concentrations of hyperforin (<1%) may not cause interactions with allopathic drugs.¹³ However, the components of St John's wort do not interfere with immunoassays used for therapeutic drug monitoring of common drugs.¹⁴ Important drug-herb interactions are summarized in Table I.

Herbal remedies and abnormal liver function tests

Kava-kava, a herbal remedy taken for anxiety, can cause severe hepatotoxicity.¹⁵ Heavy consumption of *kava* has been associated with increased concentrations of γ -glutamyltransferase (GGT), suggesting potential hepatotoxicity. Escher *et al.* described a case in which severe hepatitis was associated with *kava* use. A 50-year-old man took 3–4 capsules of *kava* daily for 2 months (maximum recommended dose: 3 capsules). His liver function tests showed a 60–70-fold increase in AST and ALT. Tests for hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis C virus (HCV) were all negative as were tests for cytomegalovirus (CMV) and HIV. The patient eventually received a liver transplant.¹⁶ In January 2003, *kava* extracts were banned in the entire European Union, Canada and the USA; the US Food and Drug Administration (FDA) strongly cautioned against using *kava*. There are at least 11 cases of serious hepatic failure and 4 deaths directly linked to *kava* extract consumption as well as 23 reports indirectly linking *kava* with hepatotoxicity.¹⁷

Chaparral can be found in health food stores as capsules and tablets and is used as an antioxidant and anticancer herbal product. However, this product can cause severe hepatotoxicity. Several reports of *chaparral*-associated hepatitis have been

TABLE I. Common drug–herb interactions

Herbal product	Interacting drug	Comments
Ginseng	Warfarin	May decrease the effectiveness of warfarin
St John's Wort	Paxil	Lethargy, incoherence, nausea
	Digoxin	Decreased AUC, peak and trough concentrations of digoxin, may reduce effectiveness of digoxin
	Cyclosporin/tacrolimus	Lower cyclosporin/tacrolimus concentrations due to increased clearance may cause transplant rejection
	Theophylline	Lowers concentration, thus decreases the efficacy of theophylline
	Indinavir, lopinavir, ritonavir, atazanavir	Lowers concentration, may cause treatment failure in patients with HIV
	Statins	Reduced plasma concentration of simvastatin but no effect on pravastatin
	Irinotecan, imatinib, R- and S-verapamil	Reduced efficacy
<i>Ginkgo biloba</i>	Oral contraceptives	Increased clearance
	Aspirin	Lower concentration, failed birth control
	Warfarin	Bleeding because <i>ginkgo</i> can inhibit platelet activating factor
<i>Kava</i>	Thiazide	Haemorrhage
	Alprazolam	Hypertension
<i>Kava</i>	Alprazolam	Additive effects with central nervous system depressants, alcohol
Garlic	Warfarin	Increases effectiveness of warfarin, bleeding
Ginger	Warfarin	Increases effectiveness of warfarin, bleeding
Feverfew	Warfarin	Increases effectiveness of warfarin, bleeding
<i>Dong quai</i>	Warfarin	Increases effectiveness of warfarin, bleeding
<i>Dan shen</i>	Warfarin	Contains coumarin, increases international normalized ratio (INR) for warfarin, causes bleeding
<i>Dan shen</i>	Warfarin	Increases effectiveness of warfarin due to its reduced elimination
Comfrey	Phenobarbital	Increases metabolism of comfrey producing a lethal metabolite, severe hepatotoxicity

reported. Gordon *et al.* reported a case where a 60-year-old woman took *chaparral* for 10 months and developed severe hepatitis for which no other cause was found. On admission her bilirubin was 12.4 mg/dl, ALT 341 U/L, AST 1191 U/L and alkaline phosphatase 186 U/L. All tests for viral hepatitis were negative. Eventually, she received a liver transplant.¹⁸

Germander has been used as a remedy for weight loss and as a general tonic. Several cases of liver toxicity have been reported in Europe due to the ingestion of germander. A 55-year-old woman taking 1600 mg per day of germander became jaundiced after 6 months. Her bilirubin was 13.9 mg/dl, AST 1180 U/L, ALT 1500 U/L and alkaline phosphatase 164 U/L. Serological tests for all hepatitis viruses were negative. Liver biopsy suggested drug-induced hepatitis. Germander therapy was discontinued and the hepatitis resolved in 2 months.¹⁹

Ginkgo and bleeding

Ginkgo biloba is prepared from dried leaves of the ginkgo tree by organic extraction (acetone/water). It is used mainly to sharpen mental focus and to improve diabetes-related circulatory disorders. The German Commission E approved the use of *ginkgo* for memory deficit, disturbances in concentration, depression, dizziness, vertigo and headache. One common reported adverse effect of *ginkgo* is bleeding. Spontaneous intracerebral haemorrhage occurred in a 72-year-old woman who was taking *ginkgo* 50 mg three times a day for 6 months.²⁰ Fessenden *et al.* reported a case of postoperative bleeding after laparoscopic cholecystectomy.²¹ Concurrent use of *ginkgo* and non-steroidal anti-inflammatory drugs (NSAIDs) as well as anticoagulants should be avoided because ginkgolide B is a potent inhibitor of platelet activating factor.

Chromium, oral anticoagulants and herbs

Athletes and body builders use chromium for improving performance. Chromium has an effect on the glucose–insulin system and can cause hypoglycaemia even in diabetics. Ginseng, whose activity has been attributed to 2%–3% ginsenosides, has been associated with hypoglycaemic properties. Fenugreek, ginger, nettle, sage and devil's claw can also affect glucose levels. Ginseng, *dan shen*, garlic, *Ginkgo biloba*, ginger, devil's claw, red clover, *dong quai* and horse chestnut increase the action of warfarin.²²

Conclusion

There are several reports of herbal remedies being contaminated with heavy metals, adulterated with allopathic medicines and containing prohibited animal and plant ingredients.²³ Lead, mercury and arsenic intoxication have been reported with the use of Ayurvedic medicines. Saper *et al.* reported that out of 70 Ayurvedic medicines tested, 13 preparations contained lead (range 5.0–37 000 µg/g), 6 contained mercury (range 28–104 000 µg/g) and/or arsenic (range 37–8130 µg/g).²⁴ Therefore, physicians need to be aware of the potential use of such herbal medicines by their patients. Abnormal laboratory tests may serve as a clue to the clinician for appropriate investigations in patients whose symptoms may be related to the use of herbal products. A multidisciplinary team approach with a pharmacist, chemical pathologist, scientific officer and physician may be appropriate to deal with toxicity and related problems due to the use of herbal medicines.²⁵

REFERENCES

- 1 Mahady GB. Global harmonization of herbal health claims. *J Nutr* 2001;**131**:1120S–1123S.
- 2 Dasgupta A, Bernard DW. Herbal remedies: Effects on clinical laboratory tests. *Arch Pathol Lab Med* 2006;**130**:521–8.
- 3 Ko RJ, Greenwald MS, Loscutoff SM, Au AM, Appel BR, Kreutzer RA, *et al.* Lethal ingestion of Chinese herbal tea containing ch'an su. *West J Med* 1996;**164**:71–5.
- 4 Panesar NS. Bufalin and unidentified substance(s) in traditional Chinese medicine cross-react in commercial digoxin assay. *Clin Chem* 1992;**38**:2155–6.
- 5 Dasgupta A, Biddle DA, Wells A, Datta P. Positive and negative interference of the Chinese medicine chan su in serum digoxin measurement: Elimination of interference by using a monoclonal chemiluminescent digoxin assay or monitoring free digoxin concentration. *Am J Clin Pathol* 2000;**114**:174–9.
- 6 Wahed A, Dasgupta A. Positive and negative *in vitro* interference of Chinese medicine Dan Shen in serum digoxin measurement: Elimination of interference by monitoring free digoxin concentration. *Am J Clin Pathol* 2001;**116**:403–8.
- 7 Osterloh J. Cross-reactivity of oleander glycosides. *J Anal Toxicol* 1988;**12**:53.
- 8 Eddleston M, Ariaratnam CA, Sjostrom L, Jayalath S, Rajakanthan K, Rajapakse S, *et al.* Acute yellow oleander (*Thevetia peruviana*) poisoning: Cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. *Heart* 2000;**83**:301–6.
- 9 Wentworth JM, Agostini M, Love J, Schwabe JW, Chatterjee VK. St John's wort, a herbal antidepressant, activates the steroid X receptor. *J Endocrinol* 2000;**166**:R11–R16.
- 10 Madabushi R, Frank B, Drewelow B, Derendorf H, Butterweck V. Hyperforin in St John's wort drug interactions. *Eur J Clin Pharmacol* 2006;**62**:225–33.
- 11 Venkataramanan R, Komoroski B, Strom S. *In vitro* and *in vivo* assessment of herb–drug interactions. *Life Sci* 2006;**78**:2105–15.
- 12 Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, *et al.* Herb–drug interactions: A literature review. *Drugs* 2005;**65**:1239–82.
- 13 Williamson EM. Interactions between herbal and conventional medicines. *Expert Opin Drug Saf* 2005;**4**:355–78.
- 14 Dasgupta A, Tso G, Szelei-Stevens K. St John's wort does not interfere with therapeutic drug monitoring of 12 commonly monitored drugs using immunoassays. *J Clin Lab Anal* 2006;**20**:62–7.
- 15 Escher M, Desmeules J, Giostra E, Mentha G. Hepatitis associated with Kava, a herbal remedy for anxiety. *BMJ* 2001;**322**:139.
- 16 Cloutre DL. *Kava kava*: Examining new reports of toxicity. *Toxicol Lett* 2004;**150**:85–96.
- 17 Anke J, Ramzan I. Kava hepatotoxicity: Are we any closer to the truth? *Planta Med* 2004;**70**:193–6.
- 18 Gordon DW, Rosenthal G, Hart J, Sirota R, Baker AL. Chaparral ingestion: The broadening spectrum of liver injury caused by herbal medications. *JAMA* 1995;**273**:489–90.
- 19 Laliberte L, Villeneuve JP. Hepatitis after the use of germander, a herbal remedy. *CMAJ* 1996;**154**:1689–92.
- 20 Gilbert GJ. *Ginkgo biloba*. *Neurology* 1997;**48**:1137.
- 21 Fessenden JM, Wittenborn W, Clarke L. *Ginkgo biloba*: A case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy. *Am Surg* 2001;**67**:33–5.
- 22 Miller LG. Herbal medicinals: Selected clinical considerations focusing on known or potential drug–herb interactions. *Arch Intern Med* 1998;**158**:2200–11.
- 23 Corns CM. Herbal remedies and clinical biochemistry. *Ann Clin Biochem* 2003;**40** (Pt 5):489–507.
- 24 Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, *et al.* Heavy metal content of ayurvedic herbal medicine products. *JAMA* 2004;**292**:2868–73.

- 25 Chan TY, Tam HP, Lai CK, Chan AY. A multidisciplinary approach to the toxicologic problems associated with the use of herbal medicines. *Ther Drug Monit* 2005;**27**:53-7.

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