

American Academy of Clinical Toxicology
Special Interest Group: Herbs & Dietary Supplements
Abstracting Service
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1. Schmidt A, Karlson-Stiber C. Caffeine poisoning and lactate rise: an overlooked toxic effect? *Acta Anaesthesiol Scand*. 2008. PMID: 18494847
Severe caffeine poisoning is rare but associated with a high mortality. The symptoms are mainly attributable to hyperadrenergic stimulation, are relatively well known and described in the literature. Transient rises in plasma lactate levels may occur but are, however, less well described. We present a case of serious caffeine poisoning with a concomitant rise in lactate treated with a non-selective beta-blocker and discuss briefly the symptomatology, the management of caffeine poisoning and the association between lactate and metabolic acidosis.
2. Etogo-Asse F, Boemer F, Sempoux C, Geubel A. Acute hepatitis with prolonged cholestasis and disappearance of interlobular bile ducts following tibolone and Hypericum perforatum (St. John's wort). Case of drug interaction? *Acta Gastroenterol Belg*. 2008;71(1):36-8. PMID: 18396749
The case of a patient under tibolone therapy for two years who developed a mixed-type liver injury with prolonged cholestasis and features of the vanishing bile duct syndrome following a ten weeks treatment with St. John wort (*Hypericum Perforatum*) infusions is reported. In the absence of evidence of a potential role for concomitant medication i.e. hydroxychloroquine sulfate to play a role in the clinical, biochemical and morphological picture, an interaction between the herbal preparation and tibolone was suspected as the likely cause of liver damage.
3. Kang L, Li B, Gao L, Li S, Wang D, Hu M, Li J. Tai-Kang-Ning, a Chinese herbal medicine formula, alleviates acute heroin withdrawal. *Am J Drug Alcohol Abuse*. 2008;34(3):269-76. PMID: 18428069
The efficacy and safety of Tai-Kang-Ning (TKN) capsule, a traditional Chinese medicine formula, for the treatment of acute heroin withdrawal syndrome were investigated by conducting a double-blind, double-dummy, positive-controlled, and randomized trial. Sixty-four patients with acute heroin withdrawal syndrome were recruited. These patients were treated with either TKN or lofexidine in a fixed schedule of doses for 10 days. The results indicate that both treatments significantly reduced withdrawal symptoms by day 3, but there was no significant difference overall between lofexidine and TKN in efficacy or safety. These results demonstrate that TKN is effective in the treatment of moderate-to-severe acute heroin withdrawal syndrome with mild adverse effects.
4. Hua Q, Zhu X, Li P, Tang H, Cai D, Xu Y, Jia X, Chen J, Shen Y. Refined Qing Kai Ling, traditional Chinese medicinal preparation, reduces ischemic stroke-induced infarct size and neurological deficits and increases expression of endothelial nitric oxide synthase. *Biol Pharm Bull*. 2008;31(4):633-7. PMID: 18379054
Refined Qing Kai Ling (RQKL) is an improved injectable multi-component preparation derived from Qing Kai Ling, which could offer the neuroprotection effect in middle cerebral artery occlusion (MCAO) model of rats by relieving the damage of vascular endothelial cell as well as inhibiting the process of inflammation. Herein, we observed whether RQKL could exert influence on the expression of endothelial nitric oxide synthase (eNOS), as a mechanism of its protective effects against ischemia. Sprague-Dawley rat model of focal cerebral ischemia was established by permanent filament occlusion of the left middle cerebral artery. We found that the administration of RQKL could reduce the ischemic infarct size as well as neurological deficit of model rats. Furthermore, it was showed that the eNOS level was consistently increased in endothelium of blood vessels of the ischemic penumbra after 2 to 72 h of permanent MCAO, and the expression of eNOS increases more in animals treated with RQKL. Our results suggested that eNOS levels in penumbral

zone were enhanced after permanent focal ischemia, and RQKL could stimulate postischemic eNOS expression, which may be an important mechanism in RQKL's protection against cerebral ischemia.

5. Lee BC, Kang SI, Ahn YM, Doo HK, Ahn SY. An alternative therapy for graves' disease: clinical effects and mechanisms of an herbal remedy. *Biol Pharm Bull.* 2008;31(4):583-7. PMID: 18379045
Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder. Antithyroid drugs have been selected as the first-line treatment of Graves' disease in Korea, Japan, and European countries. However, antithyroid drugs such as methimazole (MMI) and propylthiouracil (PTU) have limitations in clinical applications because of their side effects. In this study, we performed a clinical trial and in vitro study to investigate the clinical effects and action mechanism of Ahnjeonbaekho-tang (AJBHT), an herbal remedy for Graves' disease. In a clinical study of Graves' disease patients who had side effects from antithyroid drugs, we found that treatment by AJBHT resulted in a reduction of serum triiodothyronine (T3) and free thyroxine (FT4) levels and an increase in thyroid stimulating hormone (TSH) levels (T3: $p < 0.0001$, FT4: $p = 0.0012$, TSH: $p = 0.0370$, respectively). In vitro, AJBHT significantly inhibits FRTL-5 cell proliferation, DNA synthesis, cyclic AMP production, T4 synthesis, and the expression of thyroglobulin (Tg) mRNA in comparison with the control. These results suggest that AJBHT might suppress T(4) synthesis by modulating adenosine 3',5'-cyclic monophosphate (cAMP) and Tg expression, and therefore, AJBHT could be an alternative therapy for Graves' disease patients who have side effects from antithyroid drugs.
6. Huang WH, Hsu CW, Fang JT. Central diabetes insipidus following digestion Solanum indicum L. concentrated solution. *Clin Toxicol (Phila).* 2008;46(4):293-6. PMID: 18363121
In Taiwan, Solanum indicum L. has been used in folk medicine for the treatment of inflammation, toothache, ascites, edema, and wound infection. The plant is rich in solanine, an alkaloidal glycoside. We report a 43-year-old man who developed polyuria and polydipsia after taking seven doses of concentrated solution of Solanum indicum L. over two weeks. A water deprivation test and a low serum antidiuretic hormone level helped to confirm a diagnosis of central diabetes insipidus. We suggest that excessive doses of Solanum indicum L. may cause central diabetes insipidus.
7. Poon WT, Ng SW, Lai CK, Chan YW, Mak WL. Factitious thyrotoxicosis and herbal dietary supplement for weight reduction. *Clin Toxicol (Phila).* 2008;46(4):290-2. PMID: 18363120
This article describes three patients who developed factitious thyrotoxicosis, as well as other adverse effects, after taking herbal dietary supplements for weight reduction. All products were found to contain undeclared animal thyroid tissue and western pharmaceuticals causing the adverse effects. Adulteration is concealed addition of undeclared drugs, or other substances with therapeutic effects, to a health product. Consumption of such products, and the concealed components unwittingly, is obviously dangerous. Multiple adulterants in one product are often seen. Untoward adverse effect or drug interaction could occur. Overdose subsequent to poor standardization of the adulterants is another concern. Health care professionals must therefore be aware of the potential dangers posed by adulterated dietary supplements.
8. Wu T, Ni J, Wu J. Danshen (Chinese medicinal herb) preparations for acute myocardial infarction. *Cochrane Database Syst Rev.* 20082):CD004465. PMID: 18425903
BACKGROUND: Acute myocardial infarction (AMI) is the most important cause of morbidity from ischaemic heart disease, and is among the leading causes of death in the western world. Danshen, a Chinese herbal medicine, is widely used in China for treatment of several diseases, including AMI. OBJECTIVES: To assess the effects (both benefits and harms) of danshen preparations for AMI. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library (issue 4, 2006), MEDLINE (1966-2006), EMBASE (1980-2006), and the Chinese Biomedical Database (CBM) (1982-2006). We also handsearched 75 Chinese medical journals. SELECTION CRITERIA: Randomised controlled trials (RCTs) lasting at least 7

days were sought. Since it seemed evident that few RCTs were available, we also considered other controlled studies. DATA COLLECTION AND ANALYSIS: Eligibility and trial quality were assessed by three reviewers. MAIN RESULTS: Six studies comprised of 2368 participants were included. Only one trial was judged to be a genuine RCT and showed no statistically significant difference in reduction of total mortality (Peto OR 0.55, 95% CI 0.23 to 1.32), but a quasi-RCT reported a reduced total mortality (Peto OR 0.42, 95% CI 0.23 to 0.77). Pooling these trials yielded an approximate halving of mortality in those patients treated with danshen preparations plus usual care compared with usual care alone (Peto OR 0.46, 95% CI 0.28 to 0.75). AUTHORS' CONCLUSIONS: The evidence to support use of danshen preparations is too weak to make any judgement about its effects. Evidence from RCTs is insufficient and of low quality. The safety of danshen preparations is unproven, although some adverse events have been reported. More evidence from high quality trials is needed to support the clinical use of danshen preparations.

9. Yuan W, Wang J, Wu T. Chinese herbal medicine Huangqi type formulations for nephrotic syndrome. *Cochrane Database Syst Rev.* 20082):CD006335. PMID: 18425948
BACKGROUND: At present, there is a lack of safe and effective drugs for nephrotic syndrome (NS). Huangqi type formulations have been used to treat nephrotic syndrome for years in China, however the effects and safety of these formulations have not been systematically reviewed. OBJECTIVES: To assess the benefits and harms of Huangqi and Huangqi type formulations in treating NS in any age group, either as sole agents or in addition to other drug therapies. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles. There was no language restriction. Date of most recent search: June 2006. SELECTION CRITERIA: All randomised controlled trials (RCTs) assessing the use of Huangqi or Huangqi type formulations in treating NS in adults and children, either as sole agents or in addition to other drug therapies. DATA COLLECTION AND ANALYSIS: Two authors independently assessed study quality and extracted data. For dichotomous outcomes (remission, side effects and Inefficacy rate), results were expressed as relative risk (RR) and 95% confidence intervals (CI). Continuous outcomes (triglycerides cholesterol, plasma albumin) results were expressed as mean difference (WMD) with 95% CI. MAIN RESULTS: Three studies were identified (n = 128), all comparing Huangqi type formulations with placebo. Huangqi injection had a positive effect on plasma albumin (WMD 6.90, 95% CI 3.60 to 10.20) and cholesterol (WMD 2.13, 95% CI -2.97 to -1.29). Huangqi and red Chinese date reduced some adverse reactions (Cushing's syndrome: RR 0.55, 95% CI 0.32 to 0.94; hormone reduced syndrome: RR 0.58, 95% CI 0.39 to 0.85, respiratory tract infection: RR 0.27, 95% CI 0.08 to 0.88), but no benefit on reducing relapse. Huangqi and Danggui had a positive effect on cholesterol (WMD -0.85, 95% CI -1.70 to 0.00). AUTHORS' CONCLUSIONS: Huangqi type formulations may have some positive effects in treating NS by increasing plasma albumin and reducing blood cholesterol, Cushing's syndrome, hormone reduced syndrome and respiratory tract infection. However, limited by the lack of high quality clinical studies, we are unable to recommend Huangqi type formulations for NS. Large, properly randomised, placebo-controlled, double-blind studies are required.
10. Zhu X, Proctor M, Bensoussan A, Wu E, Smith CA. Chinese herbal medicine for primary dysmenorrhoea. *Cochrane Database Syst Rev.* 20082):CD005288. PMID: 18425916
BACKGROUND: Conventional treatment for primary dysmenorrhoea has a failure rate of 20% to 25% and may be contraindicated or not tolerated by some women. Chinese herbal medicine may be a suitable alternative. OBJECTIVES: To determine the efficacy and safety of Chinese herbal medicine for primary dysmenorrhoea when compared with placebo, no treatment, and other treatment. SEARCH STRATEGY: The Cochrane Menstrual Disorders and Subfertility Group Trials Register (to 2006), MEDLINE (1950 to January 2007), EMBASE (1980 to January 2007), CINAHL (1982 to January 2007), AMED (1985 to January 2007), CENTRAL (The Cochrane Library issue 4, 2006), China National Knowledge Infrastructure (CNKI, 1990 to January 2007), Traditional Chinese

Medicine Database System (TCMDS, 1990 to December 2006), and the Chinese BioMedicine Database (CBM, 1990 to December 2006) were searched. Citation lists of included trials were also reviewed. **SELECTION CRITERIA:** Any randomised controlled trials involving Chinese herbal medicine versus placebo, no treatment, conventional therapy, heat compression, another type of Chinese herbal medicine, acupuncture or massage. Exclusion criteria were identifiable pelvic pathology and dysmenorrhoea resulting from the use of an intra-uterine contraceptive device. **DATA COLLECTION AND ANALYSIS:** Quality assessment, data extraction and data translation were performed independently by two review authors. Attempts were made to contact study authors for additional information and data. Data were combined for meta-analysis using either Peto odds ratios or relative risk (RR) for dichotomous data or weighted mean difference for continuous data. A fixed-effect statistical model was used, where suitable. If data were not suitable for meta-analysis, any available data from the trial were extracted and presented as descriptive data. **MAIN RESULTS:** Thirty-nine randomised controlled trials involving a total of 3475 women were included in the review. A number of the trials were of small sample size and poor methodological quality. Results for Chinese herbal medicine compared to placebo were unclear as data could not be combined (3 RCTs). Chinese herbal medicine resulted in significant improvements in pain relief (14 RCTs; RR 1.99, 95% CI 1.52 to 2.60), overall symptoms (6 RCTs; RR 2.17, 95% CI 1.73 to 2.73) and use of additional medication (2 RCTs; RR 1.58, 95% CI 1.30 to 1.93) when compared to use of pharmaceutical drugs. Self-designed Chinese herbal formulae resulted in significant improvements in pain relief (18 RCTs; RR 2.06, 95% CI 1.80 to 2.36), overall symptoms (14 RCTs; RR 1.99, 95% CI 1.65 to 2.40) and use of additional medication (5 RCTs; RR 1.58, 95% CI 1.34 to 1.87) after up to three months of follow-up when compared to commonly used Chinese herbal health products. Chinese herbal medicine also resulted in better pain relief than acupuncture (2 RCTs; RR 1.75, 95% CI 1.09 to 2.82) and heat compression (1 RCT; RR 2.08, 95% CI 2.06 to 499.18). **AUTHORS' CONCLUSIONS:** The review found promising evidence supporting the use of Chinese herbal medicine for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.

11. Singh A, Rajeev AG, Dohrmann ML. Cardiomyopathy associated with ephedra-containing nutritional supplements. *Congest Heart Fail.* 2008;14(2):89-90. PMID: 18401217
12. Samuels N, Finkelstein Y, Singer SR, Oberbaum M. Herbal medicine and epilepsy: proconvulsive effects and interactions with antiepileptic drugs. *Epilepsia.* 2008;49(3):373-80. PMID: 17941846
The use of complementary and alternative medicine is on the rise, including among patients with epilepsy. Herbal medicine, one of the most popular forms of CAM, is considered to be both safe and effective by most consumers. Yet many herbs may increase the risk for seizures, through intrinsic proconvulsant properties or contamination by heavy metals, as well as via effects on the cytochrome P450 enzymes and P-glycoproteins, altering antiepileptic drug (AED) disposition. Herb-drug interactions may be difficult to predict, especially since the quality and quantity of active ingredients are often unknown. Since most patients do not inform their physicians that they are taking herbal medicines, health care professionals must initiate a dialogue in order to prevent complications with the combined regimen. At the same time, further research is required regarding the effect of herbs on seizure activity and interactions with AED treatment.
13. Kumar A. Cassia poisoning behind mysterious disease in children in uttarakhand. *Indian Pediatr.* 2008;45(5):423. PMID: 18515938
14. Das RN, Parajuli S, Jayakumar J. "Last supper with mushroom soup": a case report of amatoxin poisoning. *Mcgill J Med.* 2007;10(2):93-5. PMID: 18523612
15. Cranwell-Bruce L. Herb-drug interactions. *Medsurg Nurs.* 2008;17(1):52-4. PMID: 18429542

16. Rhabdomyolysis linked to Chinese red yeast rice. *Prescrire Int.* 2008;17(94):64. PMID: 18516816
(1) Rice fermented with "red yeast" is a traditional Chinese remedy that naturally contains various statins. Preparations based on red yeast rice are marketed as lipid-lowering medicines, often in capsule form, having the regulatory status of dietary supplements. (2) Cases of rhabdomyolysis have drawn attention to the risks associated with these products: "dietary supplement" status does not provide any guarantee as to the composition or quality of these preparations. (3) In practice, it is better to exercise caution when using plant-based dietary supplements. Patients should be informed of the risks associated with using these products, and standard drug treatments should be preferred.

17. Guzzi G, La Porta CA. Molecular mechanisms triggered by mercury. *Toxicology.* 2008;244(1):1-12. PMID: 18077077

Mercury is an ubiquitous environmental toxin that causes a wide range of adverse health effects in humans. Three forms of mercury exist: elemental, inorganic and organic. Each of them has its own profile of toxicity. Exposure to mercury typically occurs by inhalation or ingestion. Mercury can be an indoor air pollutant, however industry emission remains the most important source of inhaled mercury. Furthermore, fresh water and ocean fish may contain large amounts of mercury and dental amalgam can be another important source of inorganic and mercury vapor. The present review discusses the current information on mercury toxicity and the distinct toxicologic profile of the three forms of mercury. The existing therapeutics, new therapeutics development or agents for treating mercury poisoning will also be discussed. Since in general low levels of mercurial are tolerable, herein, we also discuss the defensive mechanisms developed by the cell to protect itself against mercury injury. This aspect may be useful to provide a biological protection against toxic effects exerted by mercury or by specific forms of mercury in view of a medicinal purpose.