JAASP



**REVIEW ARTICLE**

# Potential risks and hazards from herbal uses

Yuvadee Wongkrajang[1], Worawan Kitphati[1], Boontuim Kongsaktrakoon[1], Rungravi Temsiririrkkul [2]

[1]Department of Physiology, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand and [2]Department of Pharmaceutical Botany, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

**Key words**
herbal uses
adverse effect
herb-drug interaction

**Correspondence**
Yuvadee Wongkrajang
Department of Physiology
Faculty of Pharmacy
Mahidol University
447 Sri-ayuddhaya Road
Bangkok 10400
Thailand

**E-mail**
yuvadee.won@mahidol.ac.th

## Abstract

There are 7 types of potential risks and hazards from herbs, including allergic reactions, toxic reaction to liver and kidney, adverse effects, possible mutagenic effects, mistaken plants, contamination of heavy metals and adulterants mainly from steroids or non-steroidal anti-inflammatory drugs. In addition, herb-drug interactions related to pharmacokinetic and pharmacodynamics are also summarized. This indicates that some plants used for medicinal purposes are associated with serious risks. Therefore we should be aware in using medicinal plants.

## Introduction

Since the ancient times, herbs have not only been traditionally used as medicines for the treatment of diseases, but also taken as foods, and recently used as food supplements and nutraceuticals. Increasing demands of herbal uses with new discoveries of benefits from herbs have introduced certain ways of improper uses of herbs, potentially leading to some risks and hazards from herbs. There has been various clinical reports on adverse effects from herbs. Since 1993, US-FDA announced a warning list of herbs, i.e. Chaparral (*Larrea tridentata*), Comfrey (*Symphytum officinale*), Yohimbe (*Pausinystalia yohimbe*), Lobelia (*Lobelia inflata),* Germander (*Teucrium* genus) and Willow bark (*Salix* species), and traditional recipes, such as some Chinese traditional recipes "Jin Bu Huan" and products containing Ma huang (*Ephedra*), *Stephania* and *Magnolia* species (DHHS, 1993).

Potential risks and hazards from herbs dealing with adverse side effects which include sensitization

(and/or irritation), hepatoxicity, nephrontoxicity, mutagenicity, herb-drug interactions, etc. Improper uses of herbs may arise from incorrect handling or mistaken of the herbs or using herbs which have been contaminated and/or adulterated**.** One herb can induce more than one risks leading to several hazards. There are 7 types of potential risks and hazards classified from herbal uses, i.e. allergic reactions, toxic reactions, adverse effects, mutagenic effects, herb-drug interactions, mistaken herbs and herbal preparations, contamination and adulteration (Ernst, 1998).

**Allergic reaction:** Allergic reaction is the responses of the immune system of allergic bodies to a substance. An allergen enters the body as an invading substance which would be fought back by the body's immune system. If the body recognizes the invading substance and 'overreacts', it is hypersensitivity. The onset of allergy or hypersensitivity can be either immediate or delayed. Allergic immune responses usually separate into a period of sensitization and allergic reactions. Sensitization is induced after the immunogenic allergen induces IgE antibody which binds to tissue mast cells. Re-exposure to the allergen results in binding of the existing mast-cell-bound-IgE antibody to the allergen, followed by degranulation and activation of mediators such as histamine, prostaglandins, cytokines, etc. The symptoms of which may be skin rash, vasodilation, contraction of smooth muscle of bronchi, inflammation, etc. Skin-contact allergens may lead to skin rashes while intake allergens may result in gastrointestinal and/or vascular rashes leading to anaphylaxis. The conditions may range from very mild to severe and can be potentially fatal (Jean, 2006). During 1993-1997, hypersensitivity to royal jelly were defined from various incidences of asthma-like, bronchoconstriction, vasodilation, hypotension, allergic conjunctivitis, skin rashes with confirmed positive skin allergic tests (Thien et al, 1997, Laporte et al, 1996, Leung et al, 1997, Bullock et al, 1994, Thien, 1996). Royal jelly contains some proteins which might have stimulated IgE (Thien et al, 1997). A fatal case review of a bronchoconstriction incidence in an 11-year-old girl after receiving the second 500 mg of royal jelly to treat tonsillitis indicates a previous wheezing-sound breathing after taking the first dose (Bullock et al, 1994). Korean ginseng (*Panax ginseng* C. A. Meyer.) has been reported to cause skin rashes and Stevens-Johnson syndrome in 1 case (Faleni and Soldati, 1996).

**Hepatic and renal toxic reactions:** A list of herbs which are potentially inducers of liver damage, include comfrey, chapparal, germander and Jin Bu Huan (Barrett, 2011, Lewis, 2001, Gordon et al, 1995, Laliberte et al, 1996). Kava (*Piper methysticum* G. Forst), a remedy taken for anxiety can cause severe hepatotoxicity (Escher and Desmeules, 2001, Gow et al, 2003). Black cohosh (*Cimicifuga racemosa or Actaea racemosa*), an herb used in relieving menopausal symptoms in women, has been shown to be potentially hepatotoxic (Nisbet and O'Connor, 2007). Pennyroyal is used in folk medicine for inducing abortions, while pulegone, a constituent of pennyroyal oil, is reported to be hepatotoxic (Dasgupta A, 2010, Anderson et al, 1996).

**Table 1** Potential toxic effects associated with some common herbal medicines marketed for different indications (modified from Ifeoma and Oluwakanyinsola, 2013)

| Common name | Botanical name | Parts used | indications | Adverse effects |
|---|---|---|---|---|
| Garlic | *Allium sativum* | bulb | Anti hyperlipidimea | Bleeding, platelet dysfunction (Rose KD,1990; Petry,1995) |
| Ginkgo | *Ginkgo biloba* Linn | leaves | Circulatory disorders, improves mental alertness | Bleeding (Rowin and Lewis,1996, Rosenblatt and Mindel, 1997, Matthews, 1998) |
| Ginseng | *Panax ginseng* C.A. Mayer | roots | Relieves stress, promotes mental and physical activity central nervous system | CNS stimulation, hypertension, skin eruptions (Chan and Fu, 2007) |
| Kava | *Piper methysticum* G.Forst | roots | Sedative, anxiolytic | Sedation, oral and lingual dyskinesia, torticollis, oculogyric crisis, exacerbation of Parkinson's disease, painful twisting movements of the trunk, rash (Cupp, 1999), alter mental status and ataxia (Perez and Holmes,2005 ). |
| Kelp | *Liminaria digitata* | | Metabolic tonic, thyroid tonic, anti inflammatory | Arsenic poisoning, hyperthyroidism (Amster,2007) |
| Licorice | *Glycyrrhiza glabra* Linn | roots | Antiulcer, anti inflammatory, antihypertensive | Hypokalemic, myopathy, pseudoaldosteronism, thrombocytopenia (Celik,2012) |
| Ma-huang * | *Ephedra spp.* | | Promotes weight loss, mental and physical alertness | Hypertension, insomnia, arrhythmia, nervousness, tremor, headache, seizure, cerebrovascular event, myocardial infarction, kidney stones (Cupp, 1999) |
| *Squill* | *Urginea maritima* | bulbs | Anti-arthritic, bronchial expectorant | Symptoms resembling digitalis toxicity (Tuncok et al,1995) |
| St.John's Wort | *Hypericum perforatum* L. | Arial parts | Antidepressant, mood stabilizer | GI irritation, fatigue, dizziness, confuse, dry month (Cupp,1999) |
| Willow bark * | *Salix spp.* | Bark | Analgesic (pain killing), antirheumatic, and antipyretic | Same adverse effects as aspirin (Barrett, 2011) |
| Yohimbine * | *Pausinystalia yohimbe)* | Bark | enchanced male performance. | renal failure, seizures and death (Barrett, 2011) |

* US-FDA warning list in 1993.

Siamese senna (or Siamese cassia, Cassod tree, Thai copperpod) with its scientific name as *Senna siamea* Lam.), one of Thai well-known herbs used to treat insomnia, has been reported to cause hepatotoxic (Hongsirinirachorn et al, 2003). Siamese senna, commercially available as tablets for sedation, was shown to induce acute hepatitis in 9 patients.

Among these, 2 patients were asymptomatic with abnormal levels of hepatic enzymatic functions, while others exhibited mild to severe hepatitis. Additionally, repeated doses of Siamese senna could intro-duced remissive hepatitis in some patients (Hongsirinirachorn et al, 2003). As a consequence, Thai FDA decided to withdraw Siamese senna products from the market. Chronic liver toxicity in Wistar rats reveals dose-dependent effects on fatty liver tissues with some degeneration and necrosis (Chavalittumrong et al, 2003).

**Nephrotoxicity:** Aristolochic acid is a nephrotoxic compound found in *Aristolochia fangchi* which is an adulterant of *Stephania tetrandra* (Li et al, 2003). Aristolochic acid induced fibrosis of kidney tissue and caused adult-onset Fanconi syndrome (Lewis, 2001, Lord et al, 1999, Tanaka, 2000). *Aristolochia* species is warned as a potential risk of nephrotoxicity (Barrett, 2011). In addition, people suffering from chronic renal disease should not take alfalfa, aloe, bayberry, blue cohosh, broom, buckthorn, capsicum, cascara, coltsfoot, dandelion, ginger, ginseng, horsetail, licorice, mate, nettle, noni juice, rhubarb, senna and vervain. According to the National Kidney Foundation, herbals such as chaparral, comfrey, ephedra (Ma Huang), lobelia, mandrake, pennyroyal, pokeroot, sassafras, senna and yohimbe are unsafe (Dasgupta, 2010, Singh and Prakash, 2011, National Kidney Foundation, 2013).

**Adverse effects:** Potential toxic or adverse effects associated with some common herbal medicines which are commercially available for different indications are summarized and listed in Table 1 (Ifeoma and Oluwakanyinsola, 2013).

**Mutagenicity:** In 1998, US-FDA listed anthraquinone laxative such as senna (*Senna alexandrina*), Aloe (*Aloe vera* (L.) Burm. f.) and *Cascara sagrada* in the Category III (more data needed to determine whether they are carcinogenic) (Siegers et al, 1993). Mutagenicity of these herbs may have been shown in retrospective studies in colon cancer patients and animals (Lewis et al, 1996) but this could not related in prospective study in colon cancer (Nusko et al, 2000). Comfrey and Chapparal are also reported to be mutagenic (Stickel and Seitz, 2000, Arteaga et al, 2005)

**Herb-drug interaction:** Herbal users tend to suffer from chronic diseases which are commonly involved routine multiple drug use. Most of the chronic patients do not inform the doctors about their herbal uses. Herb-drug interactions can introduce adverse event which could be immediate or latent. Latent interaction complicates the diseases as it slowly occurs and most likely to be severe when detected (Lambrecht et al, 2001). An interaction involving the herb component causes an increase/decrease in the amount of

drug in the blood stream. Drug-herb interactions are based on the same pharmacokinetic and pharmaco-dynamic principles as drug-drug interactions (Williamson, 2003, Izzo and Ernst, 2001, Staines, 2011).
Garlic (*Alium sativum*), ginkgo (*Ginkgo biloba* Linn.), ginger (*Zingiber officinale*), turmeric (*Curcuma longa*) and ginseng are shown to interact with anticoagulant and antiplatelet drugs, i.e. warfarin and aspirin (Heck et al, 2000). St. John's Wort interferes with cyto-chrome P450 3A4 which metabolizes and, thus, reduces blood levels of cyclosporin, some protease inhibi-tors, antidepressant drugs and digoxin (Henney, 2000, Ruschitzka et al, 2000, Piscitelli et al, 2000, Lantz et al, 1999, Johne et al, 1999). Grapefruit juice inhibits cytochrome P450 3A4 resulting in increasing blood levels of drugs which are metabolized by this enzyme, for example terfenadine, calcuim channel blocker, benzodia-zepine, etc. (Bailey et al, 1994, Seden et al, 2010). Also, several kava lactones may act as inhibitors of CYP 450 system (Stickel et al, 2003). Interactions between kava and CNS depressant, alcohol, levodopa, caffeine, anticonvulsants and MAO inhibitors have been reported and summarized (Anke and Ramzan, 2004).

**Wrong herbs or improper uses:** Some of the adverse events resulted from unintentional selection of wrong herbs due to the lack of knowledge, improper collection or handling procedure and others. Different herbs may hardly be differentiable by observations and could be incorrectly collected for use. A report on a weight-control product, with a content labelled *Stephania tetrandra,* was not identificable by observations, however, using plant identification methodology the presence of *Aristolochia fangchi* was indicated and in line with the analysis finding of aristolochic acid which is a nephrotoxicant (Lewis, 2001, Lord et al, 1999, Tanaka et al, 2000).

Ebony tree (*Diospyros mollis* Griff.), Thai common name: Ma-Klua, was used in Thai traditional medicine as an effective anthelmintic. The appropriate freshly preparation of Ma-Klua has been vital to safety and effectiveness, thus, its improper use has induced eye toxicity and can lead to temporary or permanent blindness (Limpaphayom et al, 1997, Limpaphayom et al, 1980, Kitcharoen, 1981, Konsomboon, 1979,). Traditionally, fresh fruits of Ma-Klua are carefully collected and grinded. Ripen or degraded fruits, grey or brown skinned, are not used. Coconut milk, traditionally used in Thai local culture, to mix with the grinded Ma-Klua and immediately taken orally, retards gastrointestinal absorption of water-soluble forms of naphthalene or phenolic contaminants which are toxic products resulting from rapid degradation of Ma-Klua (Mahidol Medplant Database, Borsub et al, 1976). However, these phenolic contaminants were not toxic to the eyes in animal testing due to differences in metabolism.

**Contamination and Adulterants:** Contaminations and adulteration in herbal products have increasingly become a burden to Western health care system. Systemic reviews based on search engines and electronic databases led to identify some most common herb medicinal plants or products with adulterated or contaminated dust, pollens, insects, rodents, parasites, microbes, fungi, toxins, pesticides, toxic heavy

metals and/or prescription drugs. Most common adulterated drugs have been steroids and non-steroidal anti-inflammatory drugs. The most severe adverse effects caused by herbal adulterations were numerous, ranging from agranulocytosis to multi-organ failure, malignancies, heavy metal poisoning, encephalopathy, hepatorenal syndrome, nephrotoxicity, rhabdomyolysis, metabolic acidosis, renal or liver failure, cerebral edema,coma, intracerebral haemorrhage, and death. Poor quality control of herbal plantation till production of some Asian traditional remedies is the major cause of adulteration and contamination (Posadzki, 2013).

## Conclusions

This review leads to conclude that herbal products not only provide uses but might also cause some risks due to its side effects, herb adulteration, improper use or herb-drug interaction. Even though the incidence of toxicity or adverse effects from herbs was not well reported, WHO has launched warning lists of herbs to safeguard people who are using or decide to use herbal products. For safety purposes, it is necessary to check details of herbs in the product labels or leaflets before consuming. Long term use of herbs requires safeguards such as routine check for liver and renal functions at a minimum of every 3 months, if possible. If a patient decide to use herbal product as a complimentary of drug in some chronic diseases, herb-drug interaction should be concerned with close monitor. Consultation to the physician and/or the pharmacist is suggested.

## References

Amster E, Tiwary A and Schenker MB. Case report: potential arsenic toxicosis secondary to herbal kelp supplement. Environ Health Perspect. 2007; 115(4):606-608.

Anderson IB, Mullen WH, Meeker JE and Khojasteh-Bakht SC. Pennyroyal toxicity: measurement of toxic metabolites levels in two cases and review of literature. Ann Intern Med 1996; 124:726-734.

Anke J and Ramzan I. Pharmacokinetic and pharmacodynamic drug interactions with kava (Piper methysticum Forst. f.). J Enthnopharmacol 2004; 93: 153-160.

Arteaga S, Andrade-Cetto A and Cardenas R. *Larrea tridentata* (Creosote bush), an abundant plant of Mexican and US-American deserts and its metabolite nordihydroguaiaretic acid. J Ethnopharmacol 2005; 98(3):231-239.

Bailey DG, Amold JMO and Spenee JD. Grapefruit juice and drug - How significant is the interaction? Clin Pharmacokinetic 1994; 26:91-98.

Borsub L, Thebtaranonth Y, Ruchirawat S and Sadavongvivad C. A new diglucoside from the anthelmintic berries of *Diospyros mollis*. Tetrahedron Lett 1976; 2: 105-108.

Bullock RJ, Rohan A and Straatmans JA. Fatal royal jelly-induced asthma: Med J Aust 1994; 160(1):44.

Celik MM, Karakus A, Zeren C, Demir M, Bayarogullari H and Duru M, et al. Licorice induced hypokalemia, edema and throm -bocytopenia. Hum Exp Toxicol 2012; 31(12):1295-1298.

Chan P and Fu PP. Toxicity of Panax ginseng- An herbal medicine and dietary supplement. J Food Drug Anal 2007; 15(4): 416-427.

Chavittumrong P, Chivapat S, Rattnajarasroj S, Sunyasoocharee B, Soonthornchareonnon N and Panyamong S. Chronic toxicity of Cassia siamea Lam. Leaves in rats . Bull Dep Med Serv 2003; 45(3):101-104.

Cupp MJ. Herbal Remedies: Adverse Effects and Drug Interactions. Am Fam Physician 1999; 59(5):1239-1244.

Dasgupta A, Unexpected Laboratory Test Results Due to Use of Herbal Remedies. [cited 2014 Aug 10] Available from: https://www.aacc.org/resource centers/archivedprograms/expert_access/2010/october2/Documents/Dasgupta_related_article.pdf

Ernst E. Harmless herbs? A review of the recent literature. Am J Med 1998; 104(2):170-8 .

Escher M, Desmeules J. Hepatitis associated with kava, a herbal remedy. Br Med J 2001; 322: 139.

Barrett S. Illnesses and Injuries Associated with the use of selected Dietary supplements. [cited 2014 August 10] Available from: http://www. quackwatch.com/01QuackeryRelatedTopics/DSH/illnesses_and_injuries.html.

DHHS (Department of Health and Human Services). Unsubstantiated claims and documented health hazards in dietary supplement marketplace. FDA report 1993.

Faleni R and Soldati F. Ginseng as cause of Stevens-Johnson syndrome? Lancet 1996; 348 (9022): 267.

Gordon DW, Rosenthal G, Hart J, Sirota R and Baker AL. Chaparral ingestion. The broadening spectrum of liver injury caused by herbal medications. JAMA 1995; 273: 489-490.

Gow PJ, Connelly NJ, Hill RL, Crowley P and Angus PW. Fatal fulminant hepatic failure induced by a natural therapy containing kava. Med J Aust 2003; 178(9):442-443.

Gregoretti B, Stebel M, Candussio L, Crivellato E, Bartoli F and Decorti G. Toxicity of *Hypericum perforatum* (St. John's Wort) administered during pregnancy and lactation in rats. Toxicol Appl Pharmacol 2004; 200(3):201-205.

Heck AM, Dewitt BA and Lukes AL. Potential interactions between alternative therapies and warfarin. Am J Health-Syst Pharm 2000; 57:1221-1227.

Henney JE. Risk of Drug Interactions With St John's Wort. JAMA 2000;283 (13) Available from:http://www.JAMA.amaassn.org. [cited 2014 August 10]

Hongsirinirachorn M Treeprasertsuk S and Chutaputti A. Acute hepatitis associated with Barakol. J Med Assoc Thai 2003; 86(Suppl 2): S484-S489.

Ifeoma O and Oluwakanyinsola S. Screening of herbal medicines for potential toxicities. INTECH 2013. [cited 2014 August 10] Available from: http://creative commons.org/ licenses/by/3.0).

Izzo AA and Ernst E. Interactions between herbal medicines and prescribed drugs. Drugs 2001; 61(15):2163-2176.

Chapman JA, Bernstein IL, Lee RE and Oppenheimer J. Food and Allergy: a practice parameter. Annal Allergy Asthma Immunol 2006; 96: S68.

Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M and Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999; 66(4):338-345.

Kitcharoen P and Wiriyalappa C. Blindness from Ma-klua: Clinical reports of 2 patients. Chiang Mai Med Bull 1980; 19(1):5.

Konsomboon S. Blindness from Maklua. Bull Dep Med Serv Thai 1979; 4(2):59-65.

Laliberte L and Villeneuve JP. Hepatitis after use of germander, a herbal remedy. CMAJ 1996; 154: 1689-1692.

Lambrecht JE, Hamilton W and Rabinovich A. A review of herb-drug interactions: documented and theoretical. US Pharma 2001; 25(8):1-12.

Lantz MS, Buchalter E and Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatry Neurol 1999; 12(1):7-10.

Laporte JR, Ibaanez L, Vendrell L and Ballarin E. Bronchospasm induced by royal jelly. Allergy 1966; 51(6):440.

Leung R, Ho A, Chan J, Choy D and Lai CK. Royal jelly consumption and hypersensitivity in the community. Clin Exp Allergy 1997; 27(3):333-336.

Lewis CJ. FDA advises dietary supplement manufactures to remove comfrey products from market (online) 2001 [cited 2014 August 10] Available from: http://www.fda.gov/Food/RecallsOutbreaksEmergencies/SafetyAlertsAdvisories/ucm111219.htm.

Lewis CJ. Letter to health professionals regarding safety concerns related to the use of botanical products containing aristolochic acid 2001 [cited 2014 August 10] Available from: http://www.fda.gov/Food/RecallsoutbreaksEmergencies/SafetyAlertsAdvisories/ucm111200.htm

Lewis DF, Ioannides C and Parke DV. COMPACT and molecular structure in toxicity assessment: a prospective evaluation of 30 chemicals currently being tested for rodent carcinogenicity by the NCI/NTP. Environ Health Perspect 1996; 5:1011-6.

Li GD, Duke CC and Roufogalis BD. The quality and safety of traditional traditional Chinese medicines. Aust Prescriber 2003; 26(6):128-130.

Limpaphayom P, Wangsapha S and Sinjermsiri J. Treatment of optic neuritis caused by Maklue. Bull Dep Med Serv Thai 1981; 6(4):251-259.

Limpaphayom P, Wangspa S and Lilapatana P. Optic atrophy from Maklua: a case report. Siriraj Hosp Gaz 1977; 29(4): 454-457.

Lord GM, Tagore R, Cook T, Gower P, Pusey CD. Nephropathy caused by Chinese herbs in the UK. Lancet 1999; 354(9177): 481-482.

Mahidol Medplant database. Medicinal Plant for Primary Health Care: Ma-Klua. [cited 2014 August 10] Available from: http://www.medplant.mahidol.ac.th.

Matthews MKJr. Association of Ginkgo biloba with intracerebral hemorrhage. Neurology 1998; 50(6):1933-1934.

National Kidney Foundation. Use of herbal supplements in chronic kidney disease. 2013 [cited 2014 August 10] Available from http://www.kidney.org/ATOZ/atozitem.cfm?id=123

Nisbet BC and O'Connor RE. Black cohosh induced hepatitis. Del Med J 2007; 79: 441-444.

Nusko G, Schneider B, Schneider I, Wittekind C and Hahn EG. Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective case control study. Gut. 2000; 46(5):651-655.

Pattanapanyasat K, Panyathanya R and Pairojkul C. A primary study on toxicity of diospyrol and oxidized diospyrol from *Diospyros mollis* Griff. (Maklua) in rabbits eyes. J Med Ass Thai 1983; 68:60-65.

Perez J and Holmes JF. Altered mental status and ataxia secondary to acute kava ingestion. J Emerg Med 2005; 28: 49-51.

Petry JJ. Garlic and postoperative bleeding: Plast Reconstr Surg. 1995; 96(2):483-484.

Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM and Falloon J. Indinavir concentrations and St John's wort: Lancet 2000; 355(9203):547-548.

Posadzki P1, Watson L and Ernst E. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. Eur J Clin Pharmacol 2013; 69(3):295-307.

Rose KD, Croissant PD, Parliament C and Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. Neurosurgery 1990; 26(5):880-882.

Rosenblatt M and Mindel J. Spontaneous hyphema associated with ingestion of *Ginkgo biloba* extract: N Engl J Med 1997; 336(15):1108.

Rowin J and Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic Ginkgo biloba ingestion. Neurology. 1996; 46(6):1775-1776.

Ruschitzka F, Meier PJ, Turina M, Luscher TF and Noll G. Acute heart transplant rejection due to Saint John's wort: Lancet. 2000;355(9203):548-549.

Seden K, Dickinson L, Khoo S and Back D. Grapefruit-drug interactions. Drugs. 2010; 70(18):2373-2407.

Siegers CP, von Hertzberg-Lottin E, Otte M and Schneider B. Anthranoid laxative abuse--a risk for colorectal cancer? Gut 1993; 34(8):1099-1101.

Singh NP and Prakash A. Nephrotoxic Potential of Herbal Drugs. JIMSA 2011; 24(2):79-81

Staines SS. Herbal medicines: adverse effects and drug-herb interactions. J Malta College Pharm Prac 2011; 17:38-42

Stickel F and Seitz HK. The efficacy and safety of comfrey. Public Health Nutr 2000; 3(4A):501-508.

Stickel F, Baumuller HM, Seitz K, Vasilakis D, Seitz G, Seitz HK and Schuppan D. Hepatitis induced by kava (*Piper methysticum* rhizoma). J Hepatol 2003; 39:62-67.

Tanaka A, Nishida R, Maeda K, Sugawara A and Kuwahara T. Chinese herb nephropathy in Japan presents adult-onset Fanconi syndrome: could different components of aristolochic acids cause a different type of Chinese herb nephropathy? Clin Nephrol 2000; 53(4):301-306.

Thien FC, Leung R, Plomley R, Weiner J and Czarny D. Royal jelly-induced asthma. Med J Aust 1993; 159(9):639.

Tuncok Y, Kozan O, Cavdar C, Guven H and Fowler J. Urginea maritima (squill) toxicity. J Toxicol Clin Toxicol 1995; 33(1):83-86.

Williamson EM. Drug interactions between herbal medicines and prescription medicines. Drug Safety 2003; 26(15):1075-1092.

Woolf AD, Watson WA, Smolinske S, Litovitz T. The severity of toxic reactions to ephedra: comparisons to other botanical products and national trends from 1993-2002. Clin Toxicol 2005; 43(5):347-355.