Potential risks and hazards from herbal uses

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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...
Improper uses of herbs may arise from incorrect handling or mistaken use of the herbs or using herbs which have been contaminated and/or adulterated. One herb can induce more than one risk, leading to several hazards. There are seven 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 response 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, vasodilatation, 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).
### Hazards from herbs

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

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

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 (Hong-sirinirachorn 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 introduced remissive hepatitis in some patients (Hong-sirinirachorn 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, poke-root, 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
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drug in the blood stream. Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions (Williamson, 2003, Izzo and Ernst, 2001, Staines, 2011). Garlic (*Allium 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 cytochrome P450 3A4 which metabolizes and, thus, reduces blood levels of cyclosporin, some protease inhibitors, antidepressant drugs and digoxin (Henney, 2000, Ruschitzka et al, 2000, Piscitelli et al, 1999, 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, calcium channel blocker, benzodiazepine, 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 identifiable 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, Konsonmooon, 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 hemorrhage, 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


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