

Continuing Pharmacy Education

Adverse Effects Of Herbs And Drug-Herbal Interactions

Abas Hj Hussin

School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 Pulau Pinang, Malaysia.

ABSTRACT

Many people have turned away from conventional medicines, with the belief that 'natural' substances like herbs are safer than synthetic substances. This belief is augmented by many other unwarranted claims such as herbal products do not contain chemicals while conventional medicines do, thus contributing to the latter's side effects. The increasing use of herbal medicines has resulted in concern about the efficacy and safety of these products. Herbs can be hazardous in many ways. They may be intrinsically toxic or toxic when taken in combination with other preparations. Because herbal preparations are usually not evaluated for purity and consistency of active compounds, they often contain contaminants. Inclusion of incorrect but toxic species, allergens, pollen, insect parts, heavy metals such as lead, mercury and arsenic and scheduled poisons (drugs), whether intentional or unintentional, have been cited as the causes of herbal adverse reactions or toxicities. The increasing use of herbal medicines means that there is potential for more drug interactions, particularly between herbal products and conventional 'Western' medicines. Toxicity and drug-herb interaction studies are scarcely conducted and therefore should be encouraged. Proper documentation of adverse effects of herbs should be initiated and patients should be asked about their use of herbal products in order to evaluate the potential of these products to interact with concurrent prescription medications. The public should be made aware of the adverse effects of herbal products.

Keywords: herbs, adverse effects, safety, herbal toxicities, drug-herbal interactions

INTRODUCTION

Herbal medicines refer to the use of plants for the promotion of healing and maintenance of health. It is said that the use of herbal medicines originated in Egypt back in 1550 BC, yet many of their pharmacological effects remain poorly understood. Out of the estimated 800,000 plant species on Earth (1), about a quarter have been categorized and only a small fraction of these have been

examined for pharmacological efficacy. The search continues for more medications from plant sources to help treat the many diseases which still plague society.

An herb is defined as a plant or plant part used for its aromatic, savoury, medicinal or cosmetic properties. Generally, the whole plant or plant

parts are used singly or in combination with more than one plant for the purpose of treatment. However, the herbal industry now produces herbal products containing isolated chemicals or extracts of single plants in modern pharmaceutical dosage forms. This practice is against that of traditional herbal practitioners who support the use of the whole plant or plant parts, as they believe that there is synergism or antagonism among the many constituents and that the pharmacological activity depends on their combined effects.

Herbal usage

It has been estimated that 80% of the world population use some form of herbal medicine. There is little doubt that the use of herbal medicines is growing. Worldwide, the usage increases at a rate of 10-20% annually (2). It has been estimated that one third of Americans use herbal products (3) with herbal medicine sales in the United States reaching an estimated total of about US\$3.24 billion (~RM12.3 billion) in 1997. In the same year, Malaysians spent about RM2.0 billion on herbals. This amounts to about RM45.00 spent on herbals per person per year in the United States by comparison to about RM91.00 per person per year in Malaysia taking into account populations of 273 million and 22 million respectively. This illustrates the potential of the herbal market in our country. In 1999, more than 8000 herbal products were registered with the Ministry of Health. Despite the paucity of knowledge of the pharmacological efficacies of herbals, sales of tested, partially tested and untested preparations either manufactured locally or imported into Malaysia are on the rise. Of primary concern is the quality and reliability of the products available in the marketplace today since safety and efficacy prior to marketing are not guaranteed and no outside monitoring of the identity or potency of the herbals is required. This is in sharp contrast to the strict requirements and stipulations that need to be adhered to for each pharmaceutical product prior to registration.

The safety of herbal medicines is of particular importance because the majority of these products is self-prescribed and is used to treat minor and often chronic conditions. However, most patients consuming herbal preparations are not aware of the potential adverse effects these preparations may produce.

Why do people resort to herbals ?

Basically, people who use herbals can be classified into four groups:

- a) Those who solely use herbals for therapeutic purposes while dismissing the efficacy of modern medicines. This group is fast disappearing as the world becomes more develop.
- b) Those who use more herbals than conventional modern medicines for therapeutic purposes. In some cases, patients who leave mainstream medicine do so only after realizing that it has nothing more to offer in treating their health problems.
- c) Those who use more modern medicines than herbals for therapeutic purposes. This group, most probably, constitutes the majority of the Malaysian population.
- d) Those who use modern medicines and do not believe in the efficacy of herbals. Unfortunately, this group of people are unaware of the role of herbals/plants in drug development.

The first reason for the use of herbals is that it is part of the culture and belief of some people for maintenance of health or to treat certain ailments.

The second reason for the increased use of herbals is the relatively cheaper cost of herbal products and hence affordability to the lower income group. This was particularly true a few years ago, but nowadays, it is not surprising to find some herbal products in the local market which are expensive; and in fact, more expensive than modern medicines. Also, the easy availability of herbals makes them more accessible by comparison to conventional medicines where one has to obtain a prescription from a doctor. The availability of information with the advent of the Internet certainly has some effect on the increasing trend of self-medication.

The third reason is that the public has the impression of herbals being natural and that anything natural is safe. There is also this notion that herbal products do not contain chemicals and that chemicals, only found in modern medicines, are linked to toxicity, more adverse effects and hence are more harmful. Not only are these ideas propagated by irresponsible, uneducated and unscrupulous salespersons at the 'pasar malam' (night market) and bazaars, unfortunately they have also been broadcasted in privately sponsored radio programmes.

Adverse effects of herbals

It is undeniable that plants have an important role in the development of modern medicines. More than 60–70 % of modern medicines in the world market are directly or indirectly derived from plant products. In the last few years, research has uncovered interesting and beneficial chemicals in herbs. However, herbs are not non-toxic just because they are natural. Medicinal herbs contain powerful, pharmacologically active compounds. While some herbs in common use appear to be fairly safe, all medicines, herbal or otherwise, should be used with caution.

The number of reports of adverse effects of herbal medicines is now increasing due to increased use and also probably due to increased awareness among the consumers and clinical practitioners. In Malaysia, adverse effects of herbal (traditional) medicines are reported to the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC), National Pharmaceutical Control Bureau, Ministry of Health. The number of reports of adverse reactions attributable to traditional medicine has increased from 11 in 1997 to 23 in 1999. Adverse effects or poisoning pertaining to herbals reported to the National Poison Centre from 1995 to June 2000 are as follows: 8 cases (1995), 3 cases (1996), 5 cases (1997), 11 cases (1998), 7 cases (1999) and 9 cases (until June 2000). The list of herbals involved include *Datura fastuosa* ('kecubong'), *Datura metel* ('kecubong'), *Datura stramonium* ('terong pengar') *Pithecolobium jiringa* ('jering'), *Ganoderma mycelium* ('kulat kayu'), lemon grass ('serai'), margosa ('daun mambu'), nutmeg (*Myristica fragrans*), eucalyptus (*Eucalyptus globulus*), yohimbine, cassava ('ubi kayu'), camphor, stephamine, 'Air Abu Kansui', 'Minyak Rohini', 'Yu Yee' oil, 'Pil Kuda', 'Minyak Angin', 'Slimming gel' (Pusat Racun Negara – personal communication). The most common adverse effects reported are hepatic and renal problems. However, it is difficult to identify the causative agent associated with the adverse reactions encountered because traditional herbal preparations often contain multiple ingredients. The above number of reported cases most probably does not reflect the actual frequency of adverse reactions caused by traditional herbal preparations, as most cases go unreported.

Ways in which herbal preparations cause toxicity

Patients consuming herbal preparations should be aware that herbs could cause a variety of toxic

reactions. Certain groups of the population should be extra cautious as they are more susceptible to herbal adverse reactions or toxicities. They include pregnant and nursing women; some compounds in herbs can cross the placenta and are clearly linked to birth defects or other problems in newborns. Children and infants are much more sensitive than adults to the effects of all medicines including herbs. The elderly with cardiovascular problems, diabetes and other chronic diseases may show exaggerated toxic/adverse reactions to herbs. Herbs can be hazardous in many ways. The ways in which herbal products produce toxicity can be classified as follows:

- a) *Some herbals may contain toxic ingredients*
Some herbs are found to contain toxic constituents with various potential adverse effects. Pennyroyal (*Mentha pulegium*) oil contains a potent abortifacient compound and has been reported to cause both liver and kidney damage and death (4). Dobb and Edis (1984) reported neuropathy and coma in a patient who took a herbal laxative to control weight (5). The herbal laxative was found to contain podophyllin which is known to cause severe neurological symptoms. Noni (equivalent to our local 'mengkudu' or *Morinda citrifolia*) juice has been reported to contain high potassium levels and should be used with special caution in patients with renal problems because high levels of potassium may cause arrhythmias and even myocardial infarction. The consumption of various herbs such as germander (*Teucrium chamaedrys*), comfrey (*Symphytum* spp) and chapparal (*Larrea tridentata*) has been shown to be associated with hepatotoxicity and in many cases this has been attributed to pyrrolizidine alkaloids (6).
- b) *Unintentional substitution of the herb with a toxic species*
A Chinese herbal preparation used for slimming caused severe kidney damage in 105 Belgians. The herbal treatment also caused 18 cases of cancer. Investigations showed that one of the ingredients of the weight reducing pills, *Stephania tetrandra*, was replaced with *Aristolochia fangchi*, an herb related to herbs variously called birthwort, snakeroot and Dutchman's pipe. In animal studies, *Aristolochia fangchi* causes kidney damage and cancer (7-9).
- c) *Intentional addition of drugs*
The intentional addition of drugs is done to produce the therapeutic effects or potentiate

the effects of the herbals. Toxic effects of Chinese herbal preparations adulterated with drugs have been reported (10). These products were found to contain the following compounds: steroids (e.g. prednisolone, dexamethasone), pain killer (aminopyrine, acetaminophen), skeletal muscle relaxant (e.g. chlorzoxazone) minor tranquilizer (e.g. diazepam) and glybenclamide. A recent report by the Minister of Health, Malaysia, indicated that about 37% of 5000 renal problems in Malaysia might be attributed to the chronic use of traditional herbal preparations. Many of the locally available herbal preparations have been found to be adulterated with steroids, drugs, poisons and high levels of heavy metals (11). A subsequent report by the Ministry of Health stated that almost 95% of unregistered traditional herbal preparations in the local market have been found to contain steroids (12).

- d) *Environmental contamination of the herbs*
Because herbal preparations are usually not evaluated for purity and consistency of active components, they often contain unintentional contaminants. Chan et al (1977) reported cases of lead poisoning in China due to ingestion of certain Chinese herbal preparations (13). Parsons (1981) reported a case of arsenic poisoning due to contamination of yellow root herbal tea in the southern U.S. The poisoning was probably due to soil and stream contamination in the plant's natural habitat (14).
- e) *Toxic when taken in combination with modern medicines*
When herbs with some potential for toxicity are mixed with modern medicines, there may be potentiation of the toxicity of the herb by the metabolic and physiological effects of the drug. In some cases, herbal use may be contraindicated with certain disease states. Interaction of herbals with drugs may also bring about changes in the pharmacokinetic and pharmacodynamic properties of the latter. For example, herbal-drug interaction may cause decrease or increase in the absorption, distribution, metabolism and excretion of the drug. The interaction may also increase/decrease the desired pharmacological effects of the drug.

Interactions between herbs and prescription anticoagulants or antiplatelet drugs (e.g. warfarin, heparin, coumarin, and aspirin)

present perhaps the greatest risk of herb-drug interactions in modern practice. Herbal products that may potentially increase the risk of bleeding or potentiate the effects of these drugs include feverfew, garlic, ginger, ginkgo, liquorice root, parsley, turmeric, ginseng and ephedra. These herbal products have the potential to cause unexpected bleeding in patients undergoing surgery. A case report showed that *Ginkgo biloba* extract caused spontaneous bleeding into the eye from the iris within a week of daily *Ginkgo biloba* extract supplementation in a patient who had been taking aspirin to prevent myocardial infarction (15). St. John's Wort (*Hypericum perforatum*) valerian (*Valeriana officinalis*) and kava-kava (*Piper methysticum*) may prolong the effects of some anaesthetics and impair awakening from anaesthesia. A study by the National Institute of Health found that popular herbal products such as garlic and St John's Wort can decrease the effectiveness of a variety of prescription medications used to treat AIDS, some cancers, heart disease and organ-transplant patients. St John's Wort is also able to decrease the effectiveness of birth control pills by as much as 50%. Studies conducted by the author have indicated that various Malay, Indian, Chinese, Western herbal products and homeopathic preparations are able to influence the metabolism of a modern drug *in-vitro*. *Parkia speciosa*, locally known as 'petai', has been found to significantly increase liver drug metabolism *in-vitro* (16) and *in-vivo*. Studies on *Pithecallobium jiringa* ('jering') and *Pithecallobium microcarpus* ('kerdas') also showed similar significant increases in liver drug metabolism (17).

CONCLUSION

When used wisely, herbal medicines have a place in the control of certain ailments and diseases. From the above discussion, findings by many researchers have reinforced the idea that the use of natural herbal medicines may not be without risk. In the U.S., nearly 70% of patients who use herbal medicines do not inform their health care providers about their use of herbal therapies (18). More research on adverse reactions on locally available herbal preparations should be encouraged and public education on the good and bad effects of herbals need to be emphasized. Health care professionals should remain vigilant for potential interactions between herbals and prescription medications, especially when it involves

medications with narrow therapeutic indices.

ACKNOWLEDGEMENTS

A version of this paper is also available in *PRN*

Consult as part of its CPE education material. The author wishes to express his thanks to the editorial board of *PRN Consult* for allowing the article to be shared with the readers of the Malaysian Journal of Pharmacy.



REFERENCES

1. von Reis Altschul S. Exploring the herbarium. *Sci Am* 1977; 236: 96-114.
2. Phillipson JD. Global trend and market size of herbal medicine in primary health care. In: Chan KL, Hussin AH, Sadikun A, Yuen KH, Asmawi MZ, Ismail Z, editors. Trends in Traditional Medicine Research. Penang: Universiti Sains Malaysia; 1995.
3. Johnstone BA. One third of nation's adults use herbal remedies. *Herbalgram* 1997;40:49.
4. Center for Disease Control, Atlanta, Georgia. Morbidity and Mortality. *Weekly Report* 1978; 27:51.
5. Dobb GJ, Edis RH. Coma and neuropathy after ingestion of herbal laxative containing podophyllin. *Med J Aust* 1984; 140:495-496.
6. MacGregor, FB, Abernethy VE, Dahabra S. Hepatotoxicity of herbal remedies. *BMJ* 1989; 299:1156-1157.
7. Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000; 342:1686-1692.
8. Arlt VM, Pfohl-Leszakowicz A, Cosyns J, et al. Analyses of DNA adducts formed by ochratoxin A and aristolochic acid in patients with Chinese herbs nephropathy. *Mutat Res* 2001; 494:143-150.
9. Tanaka A, Nishida R, Maeda K, et al. 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; 53:301-306.
10. Anonymous. Chinese herbal medicines. *Clin Toxicol* 1975; 8:137-138.
11. Ahsan AA. Ubat tradisional turut rosakkan buah pinggang (*Traditional medicines cause kidney damage*) *Utusan Malaysia*. 2000; 5 Aug. p 2.
12. Shakri MHM. 95% ubat tradisional ada steroid (*95% Of traditional medicines contain steroids*). *Mingguan Malaysia* 2000; 3 September. p. 17.
13. Chan H, Yeh YY, Billmeier GJ, Evans WE. Lead poisoning from ingestion of Chinese herbal medicine. *Clin Toxicol* 1977; 10:273-281.
14. Parsons JS. Contaminated herbal tea as a potential source of chronic arsenic poisoning. *N Carolina Med J* 1981; 42:38-39.
15. Kleijnen J, Knipschild P. *Gingko biloba*. *Lancet* 1999; 340:1136-1139.
16. Hussin AH, Ariff AM, Husin M, Taher Y. Influence of Petai (*Parkia speciosa*, Hassk) on drug metabolism in rat liver *J Biosci* 1999; 10:7-10.
17. Hussin AH, Zulkifli M, Hadijah MT, Zainah A. *In vitro* effect of *Pithecollobium jiringa* (jering) and *Pithecollobium microcarpus* (kerdas) on hepatic drug metabolism. In: Abstract Book of the 15th Scientific Meeting of the Malaysian Society of Pharmacology and Physiology; 2000 May 8-9; Kubang Kerian: Malaysian Society of Pharmacology and Physiology, 2000. p. ORL32.
18. Eisenberg DM, Kessler RC, Foster C. Unconventional medicine in the United States : prevalence, costs and patterns of use. *N Engl J Med* 1993; 328:246-252.

Continuing Pharmacy Education questions:

Study the questions below and in the following page and send your answers (only one of A, B, C and D is correct) to the MPS-CPE Secretariat at the Malaysian Pharmaceutical Society, P.O. Box 158, Jalan Sultan, 46710 Petaling Jaya, Selangor. You may earn up to 2 CPE points.

1. What are the reasons for the shift towards more usage of herbals?

- | | |
|---|---|
| <p>A. Conventional drugs are safer than herbals.</p> <p>B. Conventional drugs are more stringently regulated.</p> | <p>C. Herbal medicines are naturally derived and hence perceived safer.</p> <p>D. Herbal medicines are naturally derived and hence perceived safer.</p> |
|---|---|

2. Which of the following is NOT true about herbal usage?
- A. Herbal usage is increasing worldwide.
 - B. On average, Malaysian individuals spend less on herbal products annually than American individuals do.
 - C. Most of the herbal medicine usage is self-prescribed.
 - D. Most herbal medicines are used to treat chronic ailments.
3. Herbal medicines are less stringently regulated because
- i. little is known about their efficacy.
 - ii. little is known about their appropriate doses.
 - iii. little is known about their adverse effects.
 - iv. little is known about interaction with modern drugs.
- A. i and ii are correct.
 - B. ii and iii are correct.
 - C. ii, iii and iv are correct.
 - D. i, ii, iii and iv are correct.
5. Herbal medicines are popular because
- i. they are relatively cheaper than most conventional drugs.
 - ii. they are more easily accessible than conventional drugs.
 - iii. they have been used, culturally, for many generations.
 - iv. they are perceived safer than conventional drugs because they are naturally derived.
- A. i and ii are correct.
 - B. i, ii and iii are correct.
 - C. ii, iii and iv are correct.
 - D. i, ii, iii and iv are correct.
4. Which of the following is NOT true about herbal products?
- A. Many herbal products often contain unintentional contaminants.
 - B. The pharmacological activity of a herbal product depends solely on one active ingredient.
 - C. Many herbal products contain plant parts of single or mixtures of plants
 - D. More than 60-70% of conventional drugs are directly or indirectly derived from plants or plant products.
6. Statistics from the Ministry of Health, Malaysia have recently indicated that the majority of the adverse effects attributable to herbal usage are
- A. hepatic and renal problems.
 - B. respiratory and renal problems.
 - C. skin and respiratory problems.
 - D. heart and skin problems.
7. The following are true about herb-drug interactions:
- i. *Gingko biloba* may increase the risk of bleeding if taken with warfarin.
 - ii. St. John's Wort may suppress the effect of general anaesthetics.
 - iii. 'Petai' has been shown to affect liver drug metabolism *in vitro*.
 - iv. Noni juice may cause problems in patients with heart problems.
- A. i and iii are correct.
 - B. ii and iv are correct.
 - C. i, iii and iv are correct.
 - D. ii, iii and iv are correct.
8. The following are ways in which herbal preparations may be toxic EXCEPT
- A. intentional addition of scheduled poisons.
 - B. unintentional contamination of the herbal products with heavy metals.
 - C. unintentional addition of scheduled poisons.
 - D. the addition of herbs with intrinsic toxic constituents.
9. In general, herbal medicines
- i. should be used with caution, just like with drugs.
 - ii. may be used to treat certain ailments provided that they are used wisely.
 - iii. usage should be monitored for interactions with drugs.
 - iv. R&D should be encouraged and the public be made more aware of its safety.
- A. i, ii and iii are correct.
 - B. i, ii and iv are correct.
 - C. ii, iii and iv are correct.
 - D. i, ii, iii and iv are correct.