

HERBAL MEDICINES: ITS TOXIC EFFECTS AND DRUG INTERACTIONS

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SUMMARY

The points of thought are why common people divert to use the Ayurvedic, Chinese and other herbal medicines? Though it is used all over the world, in India, its use is much more because of their easy accessibility, no expert consultation required, are considered safe to use and also because primary health care services fall short of peoples' need both in qualitative and quantitative terms. We should make all these easily marketed ayurvedic, and other herbal medicines FDA approved and increase public awareness about pros and cons of their uses. The common belief that anything natural is safe is not correct.

Herbal Medicines are readily available in the market from health food stores without prescriptions and are widely used in India, China, USA and all over the world. According to recent survey the majority of people who use herbal medicines do not inform their physicians about their consumptions that can cause abnormal test results and confusion in proper diagnosis. Drug herb interactions can results in unexpected concentration of therapeutic drug. Several herbal products interfere with immunoassays used for monitoring the concentrations of therapeutic drugs. Herbal medicines can also cause undesired effects. Therefore, the common belief that anything natural is safe is not correct. This review summarizes abnormal test results associated with use of herbal medicine, as well as interactions between modern western medicines and herbal products.

The US food and drug administration [FDA] mandates that only medicine have to be proven to be safe before being released into market. Herbal products do not fall under the category of drugs as long as they are not marketed for the preventions of any diseases.

Herbal products are classified as dietary supplements, and are marketed pursuant to the dietary supplements Health and Education act of 1994. Intended uses of common herbal medicines are shown in Table1. However herbal products are regulated differently in other countries. In United Kingdom any product that is not granted a license as a medical product by Medicine Control Agency, is treated as food, and no health claim or medical advice can be given on the label. Labelling of herbal products may not actually reflect the content and adverse events or interactions attributed to specific herb may be related to misidentification of plant.¹

Many commonly used herbal medicine in their irregular, high doses or with other medications in long term are toxic. Toxic effects of herbal medicines range from allergic reactions to cardiovascular, hepatic, renal, neurological and dermatologic toxic effects. The toxic effects of common herbal products are given in Table2 and Table3

Abnormal laboratory test results, toxic effects of herbal medicines and drug interactions are classified as:

A. Abnormal test results (drug concentration) due to toxic effects of the herbal products (Table2)

B. Unexpected concentration of therapeutic drug due to drug- herb interactions

C. Unexpected presence of a drug in a patient who never used that drug

Ginseng, st. John's Wort, ma-hung, kava, ginkgo biloba, dan shen, fever few, garlic, ginger, saw palmetto, comfrey, pokweed, hawthorne, dongquai, cat's claw are used by general population in USA and also in India as herbal medicine and also as domestic purpose. The most common herbal product used is Ginseng (20%) followed by Echinacea (19%), Ginkgo biloba (15%) and st. John's Wort (14%)² Different herbal medicine act different ways causing harmful effects to human physiology.

A. Abnormal test results (drug concentration) due to toxic effects of the herbal products

- Several herbal products lower the seizure threshold maintained by Phenobarbital, offsetting the beneficial anticonvulsant action of Phenobarbital. Which are:
 - Evening prime rose oil, used as remedy for premenstrual syndrome, diabetic neuropathy and attention deficit hyperactivity disorder. Evening prime rose oil contains Gamolenic acid and that lowers the seizure threshold of various anticonvulsants.³
 - Borage oil (star flower) contains also Gamolenic acid.
 - Shankpushpi an ayurvedic medicine used for epilepsy also adversely affects the effect of Phenytoin.⁴
- Warfarin is an anticoagulant with narrow therapeutic range. The drug has potentially serious consequences if bleeding complications develop, and in sub therapeutic levels may fail to protect the patient from thrombo embolic events. The herbs with documented interactions with Warfarin include Danshen, Ginseng, Siberian Ginseng, Garlic, Ginger, Clong quai, Capsicum etc.⁵ Ginseng drops the INR and Danshen cause inappropriately increased anticoagulation (Increase INR) in patients taking Warfarin.⁶ Dong Quai, a Chinese medicine used for treatment of menstrual cramps, contains coumarins which is natural vitamin K antagonists⁷
- Licorice is used as an anti inflammatory herb and also as remedy for gastric and peptic ulcers. Carbenoxolone, one of the components of Licorice, can elevate the blood pressure and cause hypokalemia⁸

B. Unexpected concentration of therapeutic drug due to drug- herb interactions

St. John's Wort is prepared from hypericum, a perennial aromatic shrub with bright yellow flowers. Many chemicals have been isolated from St. John's Wort including hypericin, pseudo hypericin, amentoflaron, flavenoids and xanthenes. Melatonin, a human pineal gland hormone is also found in St. John's Wort. St. John's Wort activates the cytochrome p-450, a mixed function oxidase liver enzyme responsible for the metabolism of digoxin and many other drugs and can result in decrease in peak digoxin concentration by 30%⁹ and reduction in indinavir a drug used in treatment of HIV. Up to 81% reduction in its concentration can lead to treatment failure.¹⁰ St. John's Wort also reduces the plasma concentration of theophylline.¹¹

C. Unexpected presence of a drug in a patient who never used that drug

Interaction of herbal and Chinese products with western medicines may cause a serious problem. Nonsteroidal anti inflammatory drug, caffeine, acetaminophen, prednisolone, benzodiazepines have been found in many Chinese medicines like Miracle herb, Tung shueb, cuifong toukuwan¹²

- Heavy metal contamination (like lead, mercury and arsenic) are found in many herbal products.¹³ Many Chinese medicine which are titled like effective in controlling epilepsy contains phenytoin¹⁴ Some medicine causes hematological abnormalities related to phenylbutazone toxicity and lead to aplastic anaemia¹⁴
- Some Chinese medicine, Zhen Qui used for diabetes mellitus which shows abnormal presence of glyburide, a sulfonylurea, and it's over dose causes profound hypoglycaemia.¹⁵
- Chan su is a major component of the traditional Chinese medicines
- Lu-Shen-Wan and Kyushin^{16,17} are used for tonsillitis, upper respiratory tract infections, palpitation, stimulation of myocardial contractions and pain relief. The cardio tonic effect of Chan su is due to its major bufadienolides, such as bufalin. Bufalin is known for vasoconstriction and vascular resistance. Its high dose causes cardiac arrhythmias.

Dan Shen is a Chinese Medicine prepared from the root of the Chinese medical plant salvia. This herb used in china and now also in USA since long for treatment of various cardiovascular diseases including angina pectoris. This compound has structural similarities with digoxin. Siberian Ginseng and Asian Ginseng has also modest interference with digoxin immunoassays.

Some herbal medicines cause abnormal laboratory results in form of alteration in liver function tests, electrolyte disturbances, blood sugar level changes, heavy metal poisoning, and alteration in thyroid profiles.

- Kava-kava is herbal sedative with an anti anxiety and calming effect having bioactive compounds include Yangonin, Kavain and dihydroxykavain.¹⁸ Kava has addictive effect with central nerves system

- depressions patients who were taking alprazolam, cimetidine and terazosin become lethargic and disoriented after kava ingestion. Kava lactones can inhibit cytochrome p450 activities and have potential for interaction for drugs metabolized in liver. Severe hepatitis associated with kava use because of toxic effect on liver the FDA warned the public against the use of kava-kava¹⁹
- Chaparral is used as an antioxidant and anticancer herbal product. Chaparral ingestion may causes hepatitis and FDA has warned public about the dangers of chaparral.²⁰
 - Mistletoe has been used as a digestive aid, heart tonic and sedatives, and Germander for weight loss and as a general tonic. In both the herbal medicine hepatotoxicity is noticed.²¹
 - Athletes and body builders use chromium for improving performance. Chromium is a trace metal that has an effect on glucose insulin system, in subject with hypoglycemia, hyperglycemia, diabetes mellitus and hyperlipidemia.²²
 - Fenugreek, Ginger, Sage, Devil's claw can also affect glucose level. Karela has been shown to improve glucose tolerance.²³
 - In females beneficial effects on the lipid profile following the Garlic oil ingestion for long time²⁴ while male had the glucose tolerance changes in using Garlic oil.
 - Licorice induced hypokalemic myopathy is reported and also increases concentration of cortisol.
 - Kelp (seaweed) tablets available in health food stores and used as thyroid tonic, an anti-inflammatory and metabolic tonic. Kelp tablets rich in vitamins and minerals also contains substandard amount of iodine which leads to hyperthyroidism.
 - Unexplained lead poisoning may occur owing to the use of herbal medicine contaminated with lead.¹³ The lead content in some Chinese medicine is found as high as 20,000 ppm.²⁵

Drug interaction at the time of surgery and anaesthesia:

Ang-Lee et al reported and recommended discontinuation of herbal or other products before proceeding for surgery and anaesthesia to avoid undesirable and unexpected side effects, complications and delayed outcome.²⁶

The American Society of Anesthesiologists suggested that patients should discontinue their medicine at least two weeks before surgery. Garlic and ginseng should be discontinued at least seven days before surgery because both herbs have been reported to aggressive bleeding.²⁶ Ginkgo biloba should be discontinued three days before surgery because it inhibits platelets aggregation causing bleeding. Kava should be discontinued at least twenty four hours before surgery because Kava can increases sedative effect of anaesthetics. Ma-hung should be discontinued at least twenty four hours before surgery because Ma-hung (EPHEDRA) increases blood pressure and heart rate. St. John's Wort should discontinue five days before surgery.

The Ginseng considered safe herbal medicine but Ginseng abuse syndrome was pointed as a result of taking ginseng more than one month. Most subject experienced central nervous system stimulation. The most effect of Ginseng on mood is dose dependant. The symptoms of ginseng abuse syndrome are hypertension, nervousness, sleeplessness, skin eruption and morning diarrhoea.²⁷

The ginkgo biloba is herbal medicine used mainly to sharpen mental focus and diabetes mellitus related circulatory disorders. The most adverse effects of ginkgo biloba are gastric irritability, headache, dizziness and spontaneous bleeding.

Garlic is domestically used in food preparation normally and its use promoted for lowering cholesterol and blood pressure. Garlic contains various sulphur containing compounds. Chopped garlic mixed with oil left at room temperature can results in a fatal botulism food poisoning according to FDA.²⁸

Ma-hung (ephedra) is commonly found in herbal weight loss products that also referred as herbal ten-phen, that with rowed from the market owing to its toxic effects. Herbal ten-phen products sometimes contains St. John's Wort and are sold as a "HERBAL PROZAC" Another ephedrine containing product can induce euphoric state named "HERBAL ECSTASY". The FDA has strongly advised consumers not to use ephedrine containing products; marketed as a street drug. The German commission contraindicated use of ephedra by patients with high blood pressure, glaucoma and thyrotoxicity.

Ephedrine, phenylalanine are the prominent alkaloids of the ephedra plants; which contains pseudoephedrine, norephedrine, norpseudoephedrine, n-methylephedrine and phenylpropolamine Toxic effects give signs and symptoms like hypertension, palpitation, tachycardia stroke and seizures. The dietary supplements that contain ephedra may pose serious health risk.²⁹

CONCLUSION

Contrary to popular belief that "natural are safe", herbal medicines can cause significant toxic effects, drug interaction and even morbidity or mortality.

This article is not a bias against herbal medicines. World wide there is resurgence of herbal remedies, and we also acknowledge their potential. The purpose of this article is to create awareness amongst clinicians regarding the use of herbal medicines by patients, and the possible complications associated with them.

Table: 1
Intended Uses of Common Herbal Medicines

Herbal Medicine	Intended Uses
Ginseng	Tonic capable of invigorating users physically, mentally and sexually, also used for dealing with stress.
Siberian Ginseng	Similar to Ginseng
St. John's Wort	Treatment of mood disorders, particularly depression
Ginkgo Biioba	Mainly to sharpen mental focus in other wise healthy adults and also in people with dementia; improvement of blood flow in the brain and peripheral circulation; treatment of diabetes mellitus related circulatory disorders, impotence and vertigo
Kava	Relief of anxiety and stress; sedative
Valerian	Treatment of insomnia
Echinacea	Immune stimulant that helps increase resistance to colds, influenza and other infections; wound healing
Garlic	To lower cholesterol levels and blood pressure; prevention of heart attack
Ginger	Prevention of motion sickness, morning sickness and nausea
Aloe	To heal wounds, burns, skin ulcers; also used as a laxative
Senna	Laxative
Cat's Claw	Immunostimulant with anti viral activities also used in AIDS, Influenza and chronic fatigue syndrome

Table: 2
Common Drug herb interactions

Herbal Product	Interacting Drug	Comments
Ginseng	Warfarin	May decreased effectiveness
Ginseng	Thenelzine	Toxic symptoms e.g. headache insomnia and irritability
St. John's Wort	Paroxetine hydrochloride	Lethargy, Nausea
St. John's Wort	Theophylline	Lower concentration and efficacy
St. John's Wort	Indinavir	Lower concentration may cause treatment failure in HIV patients
Ginkgo Biioba	Aspirin	Bleeding, can inhibit PAF
Ginkgo Biioba	Warfarin	Hemorrhage
Ginkgo Biioba	Thiazide	Hyper tension
Kava	Alprazolam	Addictive effects with CNS depressants, alcohol
Garlic	Warfarin	Increased effectiveness of Warfarin; bleeding
Ginger	Warfarin	Increased effectiveness of Warfarin; bleeding
Danshen	Warfarin	Increased effectiveness of Warfarin; bleeding
Licorice	Spironolactone	Offset the effect of Spironolactone
Shankha Pushpi	phenytoin	Lower concentration and seizure control

Table: 3
Potentially toxic drugs

Herb	Toxic effects or system affected	Intended use (Should any one use?)
Comfrey	hepatotoxic	Repairing of bone and muscles, prevention of kidney stones
Ephedra	cardiovascular	Herbal weight loss
Chan su	cardiovascular	Tonic for heart
Chaparral	hepatotoxic, nephrotoxic, carcinogenic	General cleansing tonic, blood thinner, arthritis remedy, weight loss product
Licorice	pseudoaldosterronism (sodium and water)	Treatment of peptic ulcer, hypertension, heart failure

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