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Review Article

HERBAL TOXICITIES – AN OVER VIEW

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ABSTRACT

Plants have been used since earliest period as medicines for the treatment of a range of diseases. From past few decades, plants make an important contribution to healthcare. Herbal preparations contain complex mixtures of one or more plants which contain active ingredients, plant materials in crude or processed form. The data existing for most plants to assurance their quality, efficacy and safety is unacceptable. Majority of people who use herbal medicines do not inform their physician about their use. Herbal medicines can alter physiology and these changes can be reflected in irregular test results. There are some scientific evidences are there, which proves the herbal medicines can cause considerable toxicities. So, harmonization and improvement in the process of regulation is needed for safety.

INTRODUCTION

Herbal remedies mainly obtained from the plant sources to treat various illnesses. In today's medicine, as many as one third to approximately half of all drugs available in the market are derived from plants or natural sources. For example, immunosuppressant drug cyclosporine, which is used to prevent organ rejection in transplant recipients, is derived from a soil fungus. Several anti-diabetic drugs Gymnema, Pterocarpus are also obtained from the plants. The widely used cadioactive drug digoxin is extracted from the foxglove plant (Digitalis lanata). Many herbal supplements can be used as a starting material for future drugs, but just oil needs refining and grapes needs fermentation, extensive research is needed to isolate active ingredients from the plant before they can be used as medicines.

Many plant products are toxic. In an herbal supplement, one product may produce desired therapeutic effect and other ingredients may produce toxicity, since all compounds are extracted together in making herbal supplements and good products are not usually separated from bad products, toxicity may occur the following use of common herbal supplements. In olden days, the people often chewed leaves or roots or prepared tea by boiling plant parts. Therefore, only small amounts of plant alkaloids were extracted, which may have caused lesser toxicity. Now a days, these supplements are prepared by using modern extraction techniques and most likely contain more active ingredients and may cause more toxicity. One of the reasons, some herbal supplements may because toxicity is the dose size. In general high amount of supplements

are recommended as standard dosage and such doses are not based on the scientific research. So proper control on the herbal supplements is needed[1-5].

Kava-kava[6-9]

Kava (figure-1) is prepared from a South Pacific plant (***Piper mesthysticum***). Kava is an herbal sedative anti-anxiety or calming effect, and to relieve symptoms of throat pain as it produces a "numbing" effect on the tongue and throat. The main bioactive compounds include yagonin, desmethoxyyagonin, 11-methoxyyagonin, kavin, dihydroxykavavin.

Toxicity

Kava can have additive effects with central nervous system depressants. A patient who was taking alprazolam, cimetidine and terazosin became lethargic and disoriented after ingesting kava. Kava lactones can inhibit cytochrome P-450 activities and have a potential interaction with the drugs that are metabolized by the liver. Heavy consumption of kava has been associated with increased concentrations of γ-gultamyltranferase. A 50 year old man took 3 to 4 kava capsules daily for 2 months. Liver function tests showed 60 to 70 fold increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations. Blood tests were negative for hepatitis, cytomegalovirus, and HIV. If someone has an allergy to any relative of the pepper family, such as black pepper, they have a higher chance of having a kava allergy.

Chaparral[10,11]

Chaparral (figure-2) is an evergreen shrub (***Larrea tridentata***). Leaves, stems, and bark also are available in bulk for brewing tea. Chaparral can be found in health food stores as capsules and tablets and is used as an antioxidant and an anticancer herbal product.

Toxicity

A 45 year old woman who took 160mg/d of chaparral for 10 weeks experienced jaundice, anorexia, fatigue, nausea and vomiting. The results for liver enzymes and other liver function tests were abnormally high. Viral hepatitis, cytomegaloviruses were ruled out. Liver biopsy showed acute inflammation with neutrophil and lymphoplasmacytic infiltration, hepatic disarray and necrosis.

Germander[12,13]

Germander(figure-3) is the perennial herb (***Teucrium fruiticans***). Germander has been used as a remedy for weight loss and as a general tonic. Germander tea is made from the aerial parts of the plant and has been used for centuries. Capsules made from germander powder are also available in health food stores.

Toxicity

A 55 year old woman taking 1,600mg per day germander became jaundiced after 6 months. Liver enzyme tests and other liver function tests showed increase in AST, ALT and bilirubin concentrations. Serological tests for all types of hepatitis were negative. Liver biopsy suggested drug induced hepatitis. Germander therapy was discontinued, and hepatitis resolved in 2 months (figure-4).

Kelp

Kelp (seaweed) tablets (figure-5) are available in health food stores and are used as a thyroid tonic, anti-inflammatory and a metabolic tonic. Kelp tablets are rich in vitamins and minerals but also contain a substantial amount of iodine (each tablet contains approximately 0.7 mg of iodine).

Toxicity

A 72 year old woman with no history of thyroid disease had the typical symptoms of hyperthyroidism. She had been taking 4to 6 kelp tablets a day for 1 year. After discontinuing the kelp tablets, her hyperthyroidism was resolved.

Ginseng[14]

Ginseng (figure-6) is the dried root (***Panax ginseng***). It has CNS stimulant effect. The effect of ginseng on mood seems to be dose dependent.

Toxicity

The dose of less than 15 g/d of ginseng causes depersonalization and confusion. The dose of more than 15 g/d causes ginseng abuse syndrome, which is characterized by symptoms of hypertension, nervousness, sleeplessness, skin eruption and morning diarrhea. Stevens-Johnson syndrome was observed following ingestion of ginseng at a dose of 2pills for 3 days. The recovery from this effect was occurred after 30 days. Vaginal bleeding has been reported in ginseng use. When Phenelzine taken concurrently with ginseng the following symptoms were observed insomnia, headache, irritability and visual hallucinations.

Garlic[15]

Garlic (Figure-7) consists of bulbs of the plant (***Allium sativum***). Garlic is used for its cholesterol lowering and blood pressure lowering properties. The bioactive compounds in Garlic include allyl propyl disulphide, diallyl disulphide, alliin and allicin. Allicin is sulfur containing compound.

Toxicity

Chopped garlic and oil mixes left at room temperature can result in fatal botulism food poisoning according to FDA. *Clostridium botulinum* bacteria are dispersed throughout the environment but are not dangerous in presence of oxygen. The spores produce a deadly toxin in anaerobic, low-acid conditions. The garlic and oil mixture produces that environment.

Gingko[16]

Gingko (Figure-8) consists of dried leaves of the plant (***Gingko biloba***). It is mainly used to sharpen the mental focus, improve diabetes mellitus related circulatory disorders. It is also used as a remedy for impotence and vertigo.

Toxicity

The most common adverse effects of gingko are gastrointestinal disturbances, headache and dizziness. Ingestion of 70 to 80 gingko nuts caused generalized seizures.50mg of gingko 3 times a day for 6 months ingestion results in Spontaneous intra-cerebral hemorrhage in 72 year old woman (Figure-9).

Pennyroyal[17]

Pennyroyal consists of leaves of the plant (***Mentha pulegium***). It is used as abortifacient. It is also used in treatment of fainting, flatulence, gall ailments, gout. Pennyroyal is also used in aromatherapy.

Toxicity

Pennyroyal oil contains several compounds including pulegone, a liver toxin. Pulegone is metabolized in the liver to more toxic compound methofuran.and is known to deplete glutathione in the liver. The toxicity is similar to that induced by over dose of acetaminophen. Therefore pennyroyal oil should never be ingested. Pennyroyal tea which is prepared from the same herb is also toxic and causes both hepatic and neurological damage. Interestingly, N-acetylcysteine which is used to treat acetaminophen toxicity is also useful in treating toxicity due to ingestion of pennyroyal oil. As little as 10 ml of pennyroyal oil ingestion may cause severe toxicity. It also causes skin problems.

Lectins

Lectins(Figure-10) are proteins or glycoproteins without an immune origin. These are used for blood grouping, histochemical studies, and mitogenic stimulation of lymphocytes. Lectin containing natural sources abrin (***Abrus precatorius***), kidney bean (***Phaseolus vulgaris***), horse gram (***Dolichos biflorus***). Both mistletoe (***Viscum album Linn***) and pokeroot (***Phytolacca americana***) also contains lectins.

Toxicity

Systemic exposure to pokeroot has resulted in hematological aberrations. Mistletoe may also inhibit protein synthesis.

Acorus
Acorus(Figure-11) consists of dried rhizomes of the plant (***Acorus calamus***). It contains asaraldehyde, eugenol, β-asarone, acorine. It is used as carminative, vermifuge. Volatile oil is used in perfumery, insect repellant.

Toxicity
Asarone has sedative and tranquillising properties. β-asarone has shown carcinogenic effect in animal studies. Many other culinary herbs contain low levels of β-asarone in their volatile oils and therefore the level of β-asarone permitted in permitted in food as flavouring is restricted.

Saponins
Pokeroot (***P.americana),*** the saponins found in pokeroot include phytolaccagenin and oleanolic acid (Figure-12).

Toxicity
It contains irritant saponins which have produced severe gastrointestinal irritation involving intense abdominal cramping and haematemesis. Systemic exposure to these saponins has resulted in hypotension and tachycardia. In May 1979, the US Herb Trade Association requested that all its members should stop selling pokeroot as a herbal beverage or food because of its toxicity.

Cyanogentic glycosides
These are present in the kernels of a number of fruits including apricot, Bitter almond, cherry, pear and plum seeds (Figure-13).

Toxicity
Gastric hydrolysis of these compounds following oral ingestion results in the release of HCN, which is rapidly absorbed from upper gastro intestinal tract and lead to respiratory failure. It has been estimated that 50mg HCN can be fatal, equivalent to 50-60 Apricot kernels. However, variation in cyanogenetic glycoside content of kernels could reduce or increase the number required for a fatal reaction. In early 1980s a substance called amygdalin, a cyanogenetic glycoside was promoted as a natural non-toxic cure for cancer. Two near-fatal episodes of HCN poisoning have been recorded in which the patients had consumed apricot kernels as an alternative source of amygdalin.

Furanocoumarins
These are found predominantly in the family ***Apiaceae*** (parsley, celery), ***rutaceae*** (Bergamot, citrus fruits), ***Moraceae*** and ***Fabaceae.*** The furanocoumarins occur as linear and branched forms. The most commonly reported linear furanocoumarins are 8-methoxypsoralen, 5-methoxypsolen and psoralen itself (Figure-14).

Toxicity
The furano -coumarins are phototoxic. Severe phototoxic reactions have been reported in humans following the use of bergamot oil in topical preparations.

Pyrrolizidine alkaloids
These are present in a number of plant species, notably ***Crotalaria Linn*** and ***Heliotropium Linn***.

Toxicity
These alkaloids cause severe liver damage. The hepatotoxicity is due to consumption of pyrrolizidine alkaloid constituents. Pyrrolizidine alkaloids can be divided into two categories based on their structure, namely those with an unsaturated nucleus (toxic) and those with saturated nucleus (considered non-toxic). A number of herbal remedies contain pyrrolizidines include Life root (***Senecio aureus Linn***), borage (***Borago officinalis Linn***), comfrey (***Symphytum officinale Linn***). In addition to various animal studies, two cases of hepatotoxicity associated with the ingestion of comfrey have been documented.

Ma huang (Ephedra sinica)
It is commonly found in herbal weight loss products referred to as herbal fen-phen, an alternative to fenfluramine (Figure-15).

Toxicity

The FDA has strongly advised consumer not to use ephedrine containing products marketed as alternative to scheduled drugs. Hypertension was the single most frequent adverse reaction, followed by palpitation tachycardia, stroke and seizure. Ten events resulted in death, 13 events caused permanent disability[23].

Goldenseal (Hydrastis Canadensis)

Goldenseal or orange-root is used for cough, stomach upsets, and menstrual problemand arthritis (Figure-16).

Toxicity

It is contraindicated for those taking antihypertensive medications. High amount of consumption can lead to gastrointestinal distress and possible nervous systemeffects. Drug is not recommended for pregnant and lactating woman[24].

Fever few (Tanacetum parthenium)

It is believed to be natural remedy for migraine (Figure-17).

Toxicity

It should never take with imitrex or medication, it can result in the patient's heart rate and blood pressure to raise dangerous level[25] (Figure-18).

Fig. 1: Kava kava

Fig. 2: Chaparral

Fig. 3: Germander

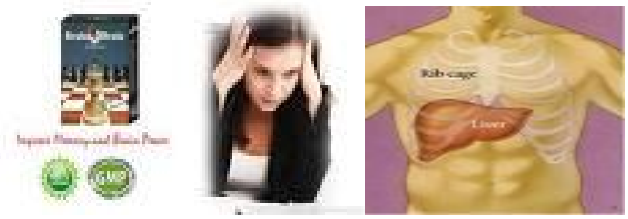

Fig. 4: toxicity of Germander

Fig. 5: kelp

Fig. 6: Ginseng

Fig. 7: Garlic

Fig. 8: Gingko

Fig. 9: toxicity of gingko

Fig. 10: Lectins

Fig. 11: acorus

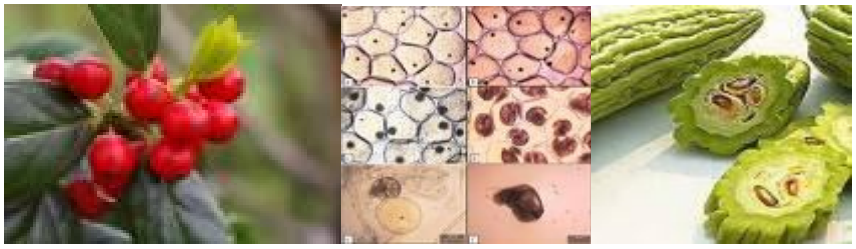

Fig. 12: Saponins

Fig.13: Cyanogenitic glycosides

Fig. 14: Furanocoumarins

Fig. 15: Ma huang

Fig. 16: Goldenseal

Fig. 17: Fever few

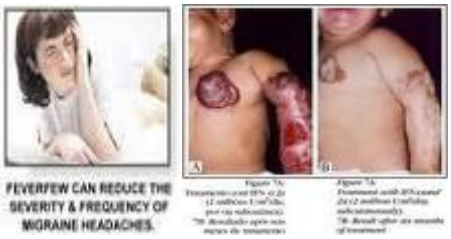

Fig. 18: toxicity of Fever few

CONCLUSION

Heavy metal contamination, adulteration, prohibited animal and plant ingredients are regularly reported in herbal remedies. The standardization techniques have uncertain effects on the safety and efficacy of final product. In general high amounts of supplements are recommended as standard dosage and such dosages are not based on scientific research. So awareness in the public about use of such herbs is necessary and to establish legal requirements for quality control of herbal remedies available to public and proper control on such drugs is needed.

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