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A Study on: Side Effects of Herbal Drugs

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ABSTRACT

A growing number of Americans are using herbal products for preventive and therapeutic purposes. The manufacturers of these products are not required to submit proof of safety and efficacy to the U.S. Food and Drug Administration before marketing. For this reason, the adverse effects and drug interactions associated with herbal remedies are largely unknown. *Ginkgo biloba* extract, advertised as improving cognitive functioning, has been reported to cause spontaneous bleeding, and it may interact with anticoagulants and antiplatelet agents. St. John's wort, promoted as a treatment for depression, may have monoamine oxidase–inhibiting effects or may cause increased levels of serotonin, dopamine and norepinephrine. Although St. John's wort probably does not interact with foods that contain tyramine, it should not be used with prescription antidepressants. Ephedrine-containing herbal products have been associated with adverse cardiovascular events, seizures and even death. Ginseng, widely used for its purported physical and mental effects, is generally well tolerated, but it has been implicated as a cause of decreased response to warfarin. Physicians must be alert for adverse effects and drug interactions associated with herbal remedies, and they should ask all patients about the use of these products. Increasingly, alternative therapies such as herbal products are being used in the United States. Approximately 25 percent of Americans who consult their physician about a serious health problem are employing unconventional therapy, but only 70 percent of these patients inform their physician of such use. Herbal products are not tested with the scientific rigor required of conventional drugs, and they are not subject to the approval process of the U.S. Food and Drug Administration (FDA). Herbal products therefore cannot be marketed for the diagnosis, treatment, cure or prevention of disease. Nonetheless, the Dietary Supplement Health and Education Act of 1994 allows these products to be labeled with statements explaining their purported effect on the structure or function of the human body (e.g., alleviation of fatigue) or their role in promoting general well-being (e.g., enhancement of mood). Analysis of some of the putative effects of herbal products shows that they sometimes closely resemble claims of clinical efficacy for various diseases or conditions. Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, some of the adverse effects and drug interactions reported for herbal products could be caused by impurities (e.g., allergens, pollen and spores) or batch-to-batch variability. In addition, the potency of an herbal product may increase the possibility of adverse effects. Because physicians are likely to encounter patients who are using herbal remedies, they need to be aware of the purported effects of these products. They also need to be cognizant of the adverse effects of herbal remedies and the possibility of deleterious drug interactions.

INTRODUCTION

In the whole world, herbal drugs are playing an important role in health care. The vast majority of medicinal herbs contain dozens of different compounds of great complexity that may modulate and modify the effects of any "active principles". Herbal medicines may produce negative effects such as allergic reactions, rashes, asthma, headaches, nausea, vomiting, and diarrhoea that can range from mild to severe. Like other prescription medications, herbal medicine should always be prescribed by a qualified and registered practitioner. Popular remedies that can cause dermatological side-effects include St John's Wort, kava, aloe Vera, eucalyptus, camphor, henna and yohimbine. Herbal remedies can cause allergic reactions and several can be responsible for photosensitization. Some herbal medicines contain arsenic or mercury that can produce typical skin lesions. Herbal products are marketed without proof of efficacy or safety that the food and drug administration requires of drugs. Herbal remedies may induce adverse Cardiac effects including sympathomimetic activity, hypertension and arrhythmias. Many interfere with platelet function, and patients at risk for bleeding or taking antiplatelets. Many herbs act during pregnancy, in various system of body such as neuroendocrine, cardiovascular system, hepatic, renal system and various metabolic and anabolic processes which may alter pharmacokinetic of other conventional drugs.

Many drugs have originated from biologically active plant chemicals, and their medicinal uses are attributed to various active chemicals found in them. Major causes of such events are adulteration of herbal products with undeclared other medicines and potent pharmaceutical substances, such as corticosteroids and non-steroidal anti-inflammatory agents. Adverse events may also arise from the mistaken use of the wrong species of medicinal plants, incorrect dosing and errors in the use of herbal medicines both by health-care providers. Consumers, interactions with other medicines, and use of products contaminated with potentially hazardous substances, such as toxic metals, pathogenic microorganisms. Due to lack of information on adverse effects of herbal medicines, inadequate reporting schemes, and inadequate information systems relating to the use of herbal medicines. WHO gives information about principles and guidelines on Quality control of herbal medicines.

CURRENT STATUS

The growing interest related to safety of herbal medicines, surveillance systems to monitor and evaluate adverse reactions associated with herbal medicines are rare. The use of some herbal supplements has been reported which are associated with oral manifestations, including ulcers, lip and tongue irritation, and swelling with feverfew, bleeding with feverfew and ginkgo, lack of sensation in tongue with Echinacea due to nerve damage, oral and lingual movement disorders with kava and salivation with Yohimbe. Recent observations indicate that all herbal medicines may not be safe since severe consequences are reported for some herbal remedies. Most herbal products in the market today have not been passed through drug approval processes to demonstrate their safety and efficacy.

Some of the herbal drugs which cause adverse reactions with other medications are:-

1. *GINGKO BILOBA*

The active ingredients found in gingko extract account for its antioxidant properties and has ability to inhibit platelet aggregation. Interaction of gingko drug with Asprin cause ocular hemorrhage .warfarin, like drugs cause interaction with gingko products.

2. ST. JOHN'S WORT

This herb is widely used as natural antidepressant and for various psychopathologic conditions which involves depression and anxiety. This inhibits receptor affinity for monoamino oxidase, dopamine and norepinephrine reuptake and its side effects include dry mouth, dizziness, and confusion, phytotoxicity, itching, lesions also seen. It cause demyelination of axons which is due to photoactivated hypericins. Nausea, weakness, allergic reactions and fatigue is also seen.

3. EPHEDRA

Ephedrine and related alkaloids are the pharmacologically active moieties of the extract of ephedrine. The extract of some species also contains pseudoephedrine. It is commonly found in herbal weight loss products. Ephedrine containing products are marketed as decongestants, bronchodilators, and stimulants. Adverse effects include induction of euphoric state, heightening of awareness and sexual sensations. It also included insomnia, nervousness, tremor, headaches, hypertension, seizures, arrhythmias, heart attack, stroke and death.

4. GINSENG

This herb is mainly used for strengthening normal body function, increasing resistance to stress and improve sexual function. Ginseng is generally well tolerated, but a probable interaction between the herb and warfarin is seen.

5. KAVA

Kava is an herbal sedative with purported antianxiety or calming effects. It is associated with extrapyramidal effects at dosage of 100 to 450 mg per day. The extrapyramidal side effects include oral and lingual dyskinesia, Painful twisting movements of the trunk, crisis and Parkinson's disease.it also shows effects with central nervous system as depressants. It should not be used with benzodiazepines, barbiturates, antipsychotics and alcohol.

NEED OF REGULATORY CONTROLS IN HERBAL DRUGS:

The side effect of herbal drugs increases when the production and sale of such products is largely uncontrolled with their improper uses. Regulatory controls are therefore considered necessary to safeguard drug interactions with herbal drugs. The risk of adverse events increases if these interfere in the way in which the body deals with these drugs.

Generally, there is a need of control in herbal drugs due to following reasons:

1) Improper use of dosage.

2) Food drug interactions.

3) Contamination and adulteration.

GENERAL ADVERSE REACTIONS DUE TO HERBAL DRUGS:-

1. Photosensitization

Essential oils used topically for aromatherapy and herbal creams have erythema like effects in exposed areas which are a cause for photosensitization. In Indian populations, contains psoralen, isopsoralen and psoralidin which are responsible for photosensitization.

2. Pellagra

Dermatological examination revealed erythematous plaques with peeling hyperpigmented borders, which were distributed symmetrically over the dorsal aspect of the limbs.

3. Arsenic dermatoses

Traditional Indian (Ayurvedic) and Chinese medicines often contain arsenic. This can be most frequent dermatological manifestations that are Bowen's disease, arsenical keratosis and squamous cell carcinoma. In the state of pregnancy, fetal growth is a template that can manifest pharmacokinetics to serious intoxication, and several cases with dermatological side-effects.

4. Sweet's syndrome

Topical herbal irritants can cause Sweet's syndrome in patients with myeloproliferative disorders which is found in topical creams containing paprika or arnica extracts. Other disorders occur with rapidly enlarging, necrotic skin lesions of the face and left leg which causes Sweet's syndrome caused by the arnica cream.

5. Mercury poisoning

Ayurvedic and traditional Chinese herbal preparations are often contaminated with mercury. This can lead to dermatological signs like tylotic eczema, dryness of the skin, skin ulceration and erythroderma.

ADVERSE EFFECTS OF HERBAL DRUGS IN DERMATOLOGY:

Asteraceae may cause contact allergic dermatitis. Other symptoms were rashes, asthmatic reactions, muscles and stomach pain. Daisies, chrysanthemum, tansy, dandelion, fever few and sunflowers all are associated with contact allergy. These adverse effects are found in massage oils, shampoos, and cosmetics. The exposed areas of the face, eyelids, neck are mainly effected. Sensitisation to certain herbs are associated with allergic reactions.

1. KAVA

Kava is a popular herbal anxiolytic of proven efficacy. Prolonged abuse of kava causes characteristic skin lesions: pigmented, dry skin covered with scales occurring most

prominently on the palms, soles, forearms, back and shins. It was also associated with extrapyramidal effects which include Dyskinesia, torticollis, painful twisting movements, crisis etc.

2. ALOE VERA

Oral and topical Aloe vera causes burning sensation after topical application, allergic contact dermatitis and mild itching. All of these adverse effects are relatively mild and reversible upon cessation of application.

3. EUCALYPTUS OIL

Eucalyptus oil is used as a remedy for various dermatological conditions. Further adverse effects are slurred speech, ataxia, muscle weakness and progressed to unconsciousness, as nausea, vomiting, diarrhoea, dizziness, muscle weakness, ataxia, tachycardia, hypotension and depression of respiration. Further suffocation and reduction in pupil size is also seen.

4. CAMPHOR

It is used as a topical anti-infective and antipruritic agent. When a person is exposed to camphor, it became ataxic and had several motor seizures. Breathing difficulties, convulsions and coma is seen after repeated topical application of camphor- containing agents for external application.

5. HENNA

Henna is a herbal preparation often used for hair colouring or as an ingredient in shampoos. The combined use of henna and p-phenylenediamine is highly toxic. Initial symptoms are angioneurotic oedema with massive oedema of the face, lips, glottis, pharynx, neck and bronchi.

6. YOHIMBINE

Yohimbine is a plant-based treatment of erectile dysfunction. Taking more than 52 mg of yohimbine three times for only 1 day resulted in itching and become scaly.

HERBAL-MEDICAL CONTRAINDICATIONS:

1. PREGNANCY

Drugs such as feverfew, chamomile, milk thistle, wormwood can stimulate uterine contraction, promotes menstruation, trigger abortions. Further, it includes are Teratogenic/Mutagenic, Uterine Vasoconstrictors, Uterine Vasodilators, Cathartics, Oxytocin Synergists, May Be Present in Milk.

2. NEUROENDOCRINE

In neuroendocrine system, some drugs lead to breakdown of enzymes. The category of drug responsible for this effect are Sympathomimetics, parasympathomimetics, anticholinergic, vasopressomimetic thyroid stimulating, thyroid depressing, aldosterone synergists.

3. METABOLIC

Anticoagulant, Cyanogenic potential, hypo-hyperglycemics

4. CARDIOVASCULAR SYSTEM CVS

Cardioglycosides, potentiating bradycardia/ hypotensive, potentiating tachycardia

5. HERBS ALTERING LIVER DRUG METABOLISM

Aristolochia serpentaria, *Artemisia tridentate*, *Berberis vulgaris*, Hydrastis are the drugs which alters normal functioning of liver enzymes.

6. HERBS THAT CAN ALTER GI ABSORPTION

Aloe, Arctostaphylos, Capsicum, Chlorophyllin, Ephedra viridis, Frangula. These drugs inhibit absorption of drugs by inhibition of metabolic enzymes and transport proteins which alters renal excretion of drugs and their metabolites.

7. IMMUNOSTIMULANTS THAT CAN RAISE WBC COUNT

Aristolochia serpentaria, *Aristolochia watsonii*, Baptisia, Commiphora.

8. HEPATIC: HERBS THAT MAY ALTER SGOT/SGPT READINGS

Anagallis, Euonymus, Mahonia, Silybum marianum alters levels of aspartate aminotransferase and alanine aminotransferases which indicates condition of liver damage.

9. PYRROLIZIDINE ALKALOID HERBS

Cacalia, *Cynoglossum officinale, Helenium hoopesii*

HERB-SPECIFIC PROBLEMS-

A- HERBS WITH MISCONCEPTIONS:

1. *Aletris farinosa*

A Human chorionic gonadotropins agonist and reproductive stimulant. Aletris is only a digestive stimulant and a source of exogenous estrogen; it instead increases utilization of endogenous estrogens.

2. Capsicum

It acts as a peripheral vasodilator, increasing blood supply to the skin and mucosa. It is not appropriate for active inflammation.1 cocaine interacts with capsicum and cause heart attack and death. It can irritate kidneys and increase pelvic blood supply which contributes to vasculitis.

3. *Cereus grandiflorus*

Like cardioactive, it moderates sinoatrial node Atrioventricular node depolarization and lessens adrenergic or drug tachycardia.

4. Corynanthe

An especially pernicious herb with simultaneous sympathetic and parasympathetic actions.

5. *Dioscorea villosa*: The first generation of synthetic steroids was made using diosgenin from Mexican yam. Wild Yam creams usually contain synthetic Natural Progesterone.

6. *Ephedra vulgaris*

It is a source of ephedrine; it is almost totally used these days as an "anorectic" or safe stimulant. Ephedrine lasts 7-8 hours, is more adrenergic, and it is easy to overlap the doses without being aware of the vascular and pulmonary stress.

7. *Ginkgo biloba*

A peripheral and cerebral vasodilator, it helps those with impaired circulation. It is often sold, as an aid to "intelligence" and is often used by students when cramming for tests, etc. Under these misguided uses it causes many headaches.

8. Hypericum

Several preliminary tests implicated it as an anti-viral for HIV. It is useful for helping some of the CNS symptoms of AIDS, but because of its antidepressant effects, not because it is antiviral.

9. Larrea

It is a hepatic depressant (excessive antioxidant activities) and can cause haemolytic-type responses if it is used well above its therapeutic window.

10. Lobelia

It shows stimulus of adrenergic-suppressed parasympathetic functions. Lobeline found in lobelia is capable of inducing vomiting and dizziness.

11. Phytolacca

It has life threatening effects such as convulsions, low blood pressure, diarrhoea, inflammatory skin conditions etc. Although useful in depressed metabolism and edematous adipose tissues, it has no fat-reducing effects, is easily toxic.

12. *Senecio aureus*

Senecios are toxic group which may cause serious liver damage. It seems to be beneficial for functional hypoestrogenic states, in herbal therapy. It is devoid of toxic pyrrolizidine alkaloids.

13. *Silybum marianum*

Various allergic reactions resulting from side effect of this herb are-swelling of lips, tongue or face, difficulty in breathing, closing of throat etc. There are hundreds of reliable biologic and medical studies that support this plant's seeds' value for mushroom poisoning, lessening the toxicity of heavy metals. Without an ongoing stress, using Silybum or its extracted silymarins can actually depress normal liver function.

14. *Viscum album*

The dried herb is sometimes not European but American Mistletoe a very different plant altogether (pharmacologically), with almost vasoconstrictive effects. Eating raw viscum can cause slowing of heart rate and even death.

B- HERBS WITH HIDDEN or THRESHOLD EFFECTS:

1. *Cannabis sativa*

It can be a strong estrogen- synergist, shortening the estrus cycle in women, antagonizing testosterone in men bad for any prostate condition.

2. *Daucus carota*

Sometimes used as a contraceptive, it contains aromatics that, in large enough quantities, can exaggerate uterine inflammation and blocks progesterone synthesis. During pregnancy, it can cause abortions.

3. *Equisetum arvense*

Use of equisetum is avoided during pregnancy. If growing in areas downstream of commercial farming, inorganic nitrates are metabolized into abnormal nicotine-like alkaloids.

4. Hydrastis

Hydrastis supplements strongly inhibits cytochrome P450 CYPD2D6 and CYP3A4/5 activity.1Topical application may cause phototoxic reaction. A mucus-membrane stimulant, useful for congested and subacute stages, it can cause inflammation if not needed, can prematurely age the placenta.

5. Valeriana

Clinical studies have found mostly headache and diarrhoea1. The dried plant, used for a long period of time, which induce a state called "Valerianism", which is a state of emotional lability generally found with bromide abuse.

DRUGS AFFECTING CARDIOVASCULAR SYSTEM-

ADVERSE EFFECTS OF COMMON HERBAL THERAPIES:

1. Hyperlipidaemia

It includes studies with deficiencies occurs with reduction in serum cholesterol of 23 mg/dl. Lipids were reduced by 15% in this subgroup randomized, placebo-controlled trials of hypercholesterolemic subjects reported reduction of only 15.7 mg/dl.

2. Hypertension

Garlic reduces blood pressure by inhibiting platelet nitric oxide synthase. Studies evaluating hypertensive subjects report a modest reduction in diastolic pressure. Large doses of garlic powder (2,400 mg) lowered blood pressure 7/16 mm Hg. Only the diastolic pressure decreased significantly.

3. Coagulation

Extract of raw garlic contains compounds that inhibit cyclooxygenase and ajoene, a compound in alcohol extracts of garlic, may inhibit binding of fibrinogen to platelet receptors. Dried garlic powder decreased platelet aggregation in controlled trials. It also elevates tissue plasminogen activator.

4. Atherosclerosis

The antiatherosclerotic activity of garlic is attributed to cholesterol lowering, by inhibition of lipid peroxidation. Garlic administered for 48 months reduced atherosclerotic plaque at the femoral artery or carotid bifurcation.

5. Vascular dementia

Ginkgo may benefit cerebrovascular disease by improving blood flow, reducing ischemia-reperfusion injury or inhibiting platelets. Patients with cognitive impairment due to diverse etiologies also with vascular dementia reported conflict in results.

6. Intermittent claudication

Ginkgo may improve intermittent claudication via vasoregulation, platelet antagonism and protection against post ischemic oxidative. A meta-analysis of pharmacologic interventions for intermittent claudication similarly concluded that ginkgo improves pain-free walking distance by 32 meters.

7. Antioxidant

Flavonoids constitute antioxidant and free radical scavenging properties, although the exact mechanism remains unclear. In addition, bilobalide and ginkgolides A and B are terpenoid compounds selectively studied for protecting ischemic tissue from reperfusion injury. Short term pretreatment with high- dose ginkgo extract (320 mg/day for five days) decreased reperfusion injury in patients undergoing aortic valve replacement.

8. Platelet antagonism

Ginkgo may inhibit platelets and platelet-induced post ischemic inflammatory response by antagonism of platelet activating factor Ginkgolide B is a potent inhibitor of platelet activating factor. Other components of ginkgo extract have been identified as inhibitors of phospholipase A2.

9. Heart failure

Ginseng is used for cardiac function, which is cardiac heart failure contrasted, resulting in hemodynamic improvement with combined therapy. Panax notoginseng plus captopril versus captopril monotherapy in patients with LV diastolic dysfunction resulted in improved diastolic relaxation with the combined medications.

10. Hypertension

Ginseng have both hypertensive and hypotensive effects. Hypotensive effects attributes to enhanced synthesis of nitric oxide. Abuse of this drug results in syndrome associated with hypertension, behavioral changes in patients and diarrohea also occur.

11. Antioxidant effects

Ginseng scavenges free radicals. An interaction of ginseng with warfarin, INR is reduced to subtherapeutic levels Interaction with digoxin, or with the digoxin assay and Siberian ginseng was found when ginseng preparations are contaminated with germanium, it causes a decrease in diuretic resistance and further leads to renal failure.

12. Heart failure

Hawthorn has few adverse effects and drug interactions. It has active compound, aescin, is a mixture of triterpene glycoside which decreases lower extremity edema by inhibition of endothelial lysosomal enzymes and causes vasoconstriction.

CONCLUSION

In general, the safety and effectiveness of alternative medicine have not been scientifically proven and remain largely unknown. The adverse effect from the herb itself, adulteration, inappropriate formulation, lack of understanding of plant and drug interactions have led to adverse reactions. To minimize the harm, it is necessary that medicines of good quality, safety and efficacy are used rationally. The risk of harm however, is less when medicines are used by informed health profession and by patients who understand responsibility of their herbal drugs. The major focus must be to empower health practitioners and patients with useful information that improves individual therapy, aids diagnosis and management of herbal drugs induced diseases. It includes accurate diagnosis of adverse drug reactions by healthcare providers and patients and surveillance of specific drug safety concerns through epidemological methods such as case control studies, record linkage, developing adverse drug reaction detection systems that could benefit patients. The supervised use and conventional medication usage will make rare side effects and interaction.

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