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Review Article

MEDICINAL PLANT POISONING AND HERB-DRUG INTERACTION: A REVIEW

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ABSTRACT

It is estimated that three quarters of the earth populace rely on herbal and conventional medicine as an origin for principal health care. Therefore, it is one of the most important and challenging errands for scientists working in drug research to examine the effectiveness of herbal medicine, to divide constructive from adverse effects, to recognize active ideology in medicinal plants and to ban poisonous plants or contaminations from herbal mixtures. In the present review, some problems are critically discussed. Botanical misidentification or mislabeling of plant material can play a role for toxic reactions in humans. Some plant descriptions in traditional herbal medicine (e.g. traditional Chinese medicine) have changed over time, which may lead to unintended intoxication by using incorrect plants. A difficulty is also the contamination of herbals with microorganisms, fungal toxins such as aflatoxin, with pesticides and heavy metals. Unprincipled processing, which differs from safe traditional preparation represents one more potential source for herbal poisoning. Unwanted effects of herbal products may also expand by the interaction of herbs with conventional drugs upon associated intake. The art of herbal medicine is to divide pharmacologically and therapeutically precious herbal drugs from harmful and toxic ones and to expand combinations of medicinal plants as safe and efficient herbal remedies. Standardization and strict control measures are essential to monitor sustainable high quality of herbal products and to exclude contaminations that badly affect patients consuming herbal medicine.

Keywords: Medicinal plant, toxicity, Herb-drug interaction, Herb-herb interaction, Traditional medicines.

1. INTRODUCTION

The herb drug interaction topic is so vast that a full volume of a book could be dedicated to it. Use of herbal products for preventive and therapeutic purposes has increased tremendously over the last two decades. More than 130 distinct chemical substances which are derived from plants are in use as drugs. Production of modern pharmaceutical compounds requires adherence to good manufacturing practice (GMP). Rigorous safety and efficacy studies are essential before getting approval from regulation bodies for human use. The same is not true with herbal drugs and supplements however this system is based more on traditional knowledge. Herbal medicines, often dispensed in a crude form of their extracts, form the mainstay of health care for a more than 50% of the population in developing countries due to either non-availability of modern medical care, its cost, or lack of health care knowledge [1]. A large portion of the population in sub-Saharan Africa depends on traditional medicine for its primary health care, whilst 50 % of the Chinese population uses herbal therapy [2]. The global annual turnover in herbal medicines is estimated at US$ 60 billion, representing approximately 20% of the overall drug market [3]. CAMs are perceived to be innocuous and safe, therefore there is ignorance of side effects or potential risks of interactions with other drug substances. Chemical compounds, present in crude herbs or their extracts, are responsible for their pharmacological actions. For example, Ginseng (*Panaxnoto ginseng*, family: Araliaceae), which is widely used in China for the treatment of various diseases like cardiovascular, neuropathy or blood disorders, is believed to be safe, though some rare side effects such as anxiety, insomnia, or pain have been reported. Also, a large number of herbal-drug interactions have been reported, e.g. ginkgo products causing bleeding or seizures [4].

The kidney is an essential organ when it comes to detoxification of the body. A large number of substances are excreted through the kidney making it vulnerable to toxins. A number of therapeutic drugs can adversely affect the kidney resulting in acute kidney injury (AKI), nephritic syndrome and chronic interstitial nephritis.

Medicinal plants are used for the treatment of various diseases (also called 'Herbal medicine' or 'phyto-medicine'). Although herbalism has a long tradition of use outside conventional medicine, it is becoming more mainstream as improvements quality control, and clinical research, show the value of herbal medicine in treating and preventing disease. In general, four types of herbal medicine exist: Asian, European, Indigenous, and Neo-Western. The Asian and European systems go back thousands of years, appear in pharmacopoeia, and with such a tradition of use, are better understood than those of indigenous origins that are often only orally recorded [5]. Pharmacopoeia is an official book published usually under the jurisdiction of the government and which contains a list of drugs, their formulas, and methods of identification, requirements and tests for their strength and purity, and other related information. The ones which are most established are of Asian origin, particularly from India (Aryuvedic, Unani, Siddha), China (Wu-Hsing), and Japan (Kampo). Regulatory bodies of various countries have become conscious about the various aspects of herbalism and thus prepared official monographs of these medicines regarding their identity, purity, and analysis. In India a well-established ministry (Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy (AYUSH)) looks after these five systems of indigenous medicines that are widely practiced in India. For every system of medicine, there is an official pharmacopoeia, for instance, India has Unani Pharmacopeia, and Aryuvedic pharmacopoeia. America has the American Herbal Pharmacopoeia. In the Pharmacopoeia of the People's Republic of China (PPRC) volume 1 covers the Traditional Chinese Materia Medica, including Traditional Chinese Patent Medicines, while Volume 2 is dedicated to conventional pharmaceuticals. The concomitant use of herbal medicines and modern medicine is wide spread globally because of the ready availability. The clinical consequence of herb-drug interactions varies, from being well-tolerated to moderate or serious adverse reactions, even possibly life-threatening. They reported the possible interactions between seven popular herbal medicines: ginkgo, ginseng, St John's wort, Echinacea, garlic, saw palmetto, and kava, and conventional drugs. They found that St John's wort (*Hypericum perforatum*), reduces the plasma concentrations (and/or increases the clearance) of alprazolam, amitriptyline, ciclosporin, atorvastatin, chlorzoxazone, debrisoquine, erythromycin, digoxin, fexofenadine, gliclazide, imatinib, indinavir, ivabradine, mephenytoin, methadone, midazolam, omeprazole, oral contraceptives, quazepam, simvastatin, talinolol, verapamil, voriconazole, and warfarin via cytochrome P450 (CYP) and/or P-glycoprotein induction. Ginkgo (Ginkgo biloba) was found to decrease the plasma concentrations of omeprazole, ritonavir and tolbutamide. Clinical cases indicate interactions of ginkgo with antiepileptics, aspirin (acetylsalicylic acid), diuretics, ibuprofen, etc. Kava (*Piper methysticum*) increases the clearance of chlorzoxazone (a CYP2E1 substrate) and may interact with levodopa, alprazolam, and paroxetine. Ginseng (*Panax ginseng*) may interact with phenelzine and warfarin. Garlic (*Allium sativum*) interacts with chlorpropamide, fluindione, ritonavir and warfarin; it also reduces plasma concentrations of chlorzoxazone (a CYP2E1 probe). Since herbal products are not regulated for purity and potency like conventional drugs, it is possible that some of the adverse effects and herb-drug interactions reported could be due to impurities present or product variability.

2. CAUSES OF HERBAL TOXICITY

Herbal toxicity can develop through incorrect identification leading to substitution of an innocuous herb with a toxic one; consumption of a herb with unknown toxicity; or deliberate or inadvertent contamination with nephrotoxic non-herbal drugs (e.g. non-steroidal anti-inflammatory agents), pesticides or chemicals (e.g. heavy metal contamination from soil or water); or potentiation of the toxic effect of a conventional drug due to interaction with a compound present in the herb; or consumption of meat from an animal that has grazed on toxic plants (e.g. hemlock). The kidney is the route of excretion of most of the substances present in the herbs. The high blood flow and large endothelial surface area of the kidneys ensures delivery of large amounts of toxin to the renal parenchyma. High concentrations may be reached in the medulla because of active tubular transport, especially during a state of fluid deprivation. Renal involvement associated with the use of traditional medicinal products can take several forms including acute kidney injury, tubular function defects, dyselectrolytaemias, systemic hypertension, chronic kidney disease (CKD), renal papillary necrosis, urolithiasis and urothelial cancer [6-9].

Commonly, medicinal plants contain bioactive compounds which exhibit both intra and inter species difference in type and content. Plants by virtue of their chemical constituents are potentially toxic; thus, some plants used in traditional medicine are intrinsically toxic. Some plants well known in traditional medicine to be toxic or poisonous include *Atropa belladonna*, Datura spp.,

Digitalis spp. [10].

Many plants used in traditional medicine or used as food have established some toxicity (mutagenic and carcinogenic) effects [11]. On the other hand, some of the toxic plants are useful to man as medicines and also as poisons for hunting and for use as pesticides, for example, Datura (tropane alkaloids), Digitalis (cardiac glycosides) and Pyrethrum (pyrethrin insecticides) [12]. Well known medicinal plants have demonstrated toxicity in laboratory studies and field observations. For example, Lantana camara used in the organization of malaria and other diseases has been reported to be hepatotoxic in numerous animal species which could be of concern concerning its chronic use in man [13].

3. MECHANISMS INVOLVED IN HERB-DRUG INTERACTIONS

The mechanisms and clinical implications of herb-drug interactions are well recognized [14]. Pharmacokinetic interactions are caused by alterations in the absorption, distribution, metabolism, or excretion of drugs which results in altered levels of the drug or its metabolites.

3.1. Interaction with Efflux Transporters

The efflux transporters play a role in limiting influx of xenobiotics, thus preventing the intracellular accumulation of their own substrates. The activity of the efflux transporters on interaction with herbs may be subdued by competitive or non-competitive mechanisms, which may potentially escort to toxic blood plasma concentrations of drugs that are normally substrates. Conversely, the induction of efflux transporters by herbs would result in sub therapeutic plasma drug levels important to treatment failure. For example P- Glycoprotein (P-gp), a multi drug confrontation protein, plays an significant role in regulating the absorption/reabsorption, distribution and abolition of many therapeutic agents. P-gp affects oral drug absorption and decreases bioavailability by pumping back the drug molecules into the gastrointestinal tract lumen. In hepatocytes, most of the substances are pumped into the bile by P-gp and this efflux occurs in many other organs including kidney as well [15]. Phytoconstituents may inhibit or induce P-gp which will in turn, decreases/potentiates the substrate-induced-fit of drugs resulting in even much slower/higher efflux of most P-gp substrates [16]. P-glycoprotein confers high levels of resistance to bulky amphipathic natural product type drugs such as paclitaxel, Vinca alkaloids, anthracyclines, camptothecins, and epipodophyllotoxins. Alisol B23-acetate from Alisma orientalis enhances anticancer activity of vinblastine, doxorubicin, rhodamine-123 by reducing P-gp efflux activity in vitro in MDR cell lines (HepG2-DR and K562-DR) (van Asperen et al., 2000). Citrus paradise (Grape fruit juice) has been reported to inhibit P-gp rhodamine-123 efflux in vivo in healthy volunteers. It was also found to increase the bioavailability of nifedipine in vivo in rats and talinolol in vitro in Caco-2 cells [17-18]. Other efflux transporters are the Multi-drug Resistance-associated Protein-2 (MRP2) or Breast Cancer Resistance Protein (BCRP). MRP2 is localized in the bile canalicular membrane of hepatocytes, and exports relatively large hydrophilic compounds like the glutathione, glucuronide and sulfate conjugates of endogenous and exogenous compounds from liver cells into the bile [19]. MRP2 is also responsible for the biliary secretion of glucuronide, acetaminophen and camptothecin. Therefore, possible interactions of these with herbs or drugs affect the functioning of MRP2, i.e. there may be an increased effect of drugs which are effeluxed by this system [20]. It is believed that herbs that show an ability to modulate P-gp activity which may also affect related efflux transporters. Some plant-derived polyphenols that interact with P-gp can also modulate BCRP activity *in vitro*. Flavonoids like apigenin, genistein, biochanin A, and kaempferol from Silybum marianum, inhibits BCRP thereby enhancing the accumulation of the BCRP substrate mitoxantrone [21]. Naringin, a phytochemical in *Citrus paradisi* juice, inhibits the influx or uptake of active transporter organic anion transporting polypeptide (OATP) 1A2 consequently lowering the bioavailability of certain drugs [23, 23]. Inhibition of OATP1 and OATP3 by components of *Citrus sinensis* and *Malus domestica* juices may decrease drug uptake and lead to sub-therapeutic drug concentrations whilst over-induction of OATP may increase drug uptake and lead to toxic blood drug concentrations [24].

3.2. Herb-Drug Interactions at Metabolism Level

Pharmacokinetic herb-drug interactions occur when drug metabolic enzymes are induced or inhibited by concomitant herbal medicines. For example, induction of CYP enzymes often results in therapeutic failure because of lower plasma concentrations of the drugs. One of the well-studied herbal medicines, St. John's Wort (*Hypericium perforatum*), induces CYP3A4 and CYP2B6, resulting in a decrease in plasma levels of irinotecan and imatinib, which are two chemotherapeutic drugs. In general, inhibition of CYP enzymes would lead to an increase in plasma concentrations of the concomitant

drug, and increased toxicity. Furano coumarins (e.g., naringenin and bergamottin) in paradisi juice, and C. sinensis increase the plasma concentration of a number of drugs, including cyclosporine, terfenadine, midazolam and felodipine, through mechanism-based inhibition of the CYP3A4 enzyme as 'suicide substrate' in vitro and in vivo. Some herbs such as meadowsweet and black willow, which contain pain-reducing salicylates, may displace highly protein bound drugs such as warfarin and carbamazepine, thus increasing the adverse effects of these drugs [25].

3.3. Herb-Drug Interactions at Elimination Level

The major routes for the elimination of drugs remain via the kidney and bile, but there are no significant herb-drug interactions through bile elimination. Drugs that are chiefly excreted by the kidneys are involved in herb-drug interactions by different mechanisms such as competition at active transport sites, or alterations in glomerular filtration, passive renal tubular reabsorption or active secretion and urinary pH [26]. The mechanism of herbal diuresis is complex and non-uniform. Certain herbs increase the glomerular filtration rate but do not stimulate electrolyte secretion, while others act as direct tubular irritant [27]. For example, Impila (*Callilepis laureola*) causes damage to the proximal convoluted tubules and the loop of henle [28]. Whilst uvaursi (*Arctostaphylos uva*), dandelion (*Taraxacum officinale*), goldenrod (*Solidago virgaurea*), juniper berry (*Juniperus communis*), parsley (*Petroselinum crispum*), horsetail (*Equisetum arvense*), asparagus root (*Asparagus officinalis*), and alfalfa (*Medicago sativa*) have been found to have diuretic properties and may increase the renal elimination of other drugs [28]. Pharmacodynamic Interactions Pharmacodynamic interactions are herb-drug interactions that cause changes in pharmacological responses. Herb-drug pharmacodynamic interactions involve changes in the pharmacological effects of the drug through additive, synergistic or antagonistic actions [29]. Any single herbal preparation contains several components, many of them having unknown biological activities; therefore, a herbal medicine can potentially mimic, increase, or reduce the effects of co-administered drugs through simultaneous effects on the same drug targets. Toxicity may occur if the effect of the drug in combination with the herbal medicine is enhanced synergistically or by additive effects. For example, ginger, garlic, ginseng, alfalfa, ginkgo, chamomile (*Matricaria recutita*), and danshen may enhance the anticoagulant activity of warfarin by targeting the same vitamin K epoxide reductase target [30]. *Aspilia africana*, when used along with artemisinin, or chloroquine for malaria, has been reported to antagonize their effects [31]. Ephedra is known to have risk for myocardial ischemia, tachycardia, hypertension and it may also produce ventricular arrhythmias when combined with anesthetics [32].

3.4. Herbal drug interactions

Herbal drug interactions and possible effects a book published by WHO listed some of the well-established interactions between herbs and conventional drugs. Numerous examples are available in the literature, such as cranberries, known for their vitamin C content, increasing the effect of blood thinners (anticoagulants) like warfarin, leading to bruising or bleeding. If an herb inhibits or induces cytochrome P450 enzyme, it will show effects on other drugs which are metabolized by that enzyme. For example, warfarin is affected by herbs e.g. *Carica papaya*, Harpago-phytum that inhibit cyto-chrome P450. Herb-herb interactions are also reported such as the incompatibility of licorice with sargassum, veratrum with scrophularia, and raw aconite with raw pinellia. Aconite has hypotensive, diuretic, cardiac, depressant activities [33] and raw aconite or pinellia products are extremely toxic. The aconite alkaloids have a narrow therapeutic index. *Pinellia ternata* was banned in 2004 in the US because of the presence of ephedrine alkaloids. These chemicals might cause serious side effects, such as heart attacks, stroke, or seizures. The combination of sargassum and glycyrrhizae has some toxic effects on rats' white blood cell and cardiac muscle and there is a correlation between toxicity and dose [34]. Herbs which reduce the effect of each other are also known such as raphanus which inhibits the action of ginseng; whilst ginseng inhibits that of pteropus. Similarly, clove affects the action of curcuma. Table 1 summarizes the drug interaction of herbal drugs used in treatment of kidney disorders. Meanwhile, Table 2 discusses the herbs that produce various undesirable/ unwanted effects if used with other modern medicines.

Plant herb	Pharmacological effect	Possible interaction with other drugs or herb	Possible outcomes	References
Agrimony (*Agrimonia*	uricolytic effect, diuretic effect,	May increase the risk of bleeding when taken with aspirin, anticoagulants (e.g.	Experimental studies in mice show limited	[35]

eupatoria)	hypotensive effect, hypoglycemic effect	warfarin, heparin), anti-platelet drugs (e.g. clopidogrel) and non-steroidal anti-inflammatory drugs (NSAIDS) (e.g. ibuprofen). May lower blood sugar levels and blood pressure. Possible additive effect with hypotensive drugs contains up to 21% tannins, chronic ingestion may result in nephrotoxicity Experimental	evidence of a possible blood glucose lowering effect. There are no reported cases of decreases in clotting time.	
Cordyceps sinensis	Known to increase immunity Hypoglycemic effect bronchitis, asthma, COPD	All Immunosuppressant drugs Antidiabetic drugs May affect drugs used in lung diseases	Impairs intended immuno-suppressive effects Potential for hypoglycemia, or diabetic shock	[36]
Equisetum arvense L. (Horsetail)	Urinary antiseptic, diuretic, urolithiasis, cholelithiasis, hemostatic, stops bleeding, Anxiolytic, hypoglycemic, hepatoprotective and free radical scavenging activities.	Digitalis, Furosemide, CNS stimulants (e.g. caffeine), diabetic, gout, and hypertensive agents	Anxiolytic effect of cardiac stimulants (e.g. digitalis) as may potentiate their effect. Concurrently with diuretics can cause potassium loss (hypokalemia). Combining with CNS stimulants may cause over stimulation of the central nervous system May lead to diabetic shock increases production of uric acid and dieresis	[37]
Aloe vera gel and juice	Insulin or oral hypoglycaemic agents	Potentiation in hypoglycemic effect	Clinical studies and case report	[38]
Bitter melon (*Momardica charantia*)	Insulin or oral hypo-glycaemic agents	Potentiation in hypoglycemic effect	Clinical studies	[39]
Chasteberry fruit (*Vitex agnus-castus*)	Metoclopramide	Might potentiate the actions of dopaminergic agonists (e.g. bromocriptine, levodopa), therefore counteracts dopaminergic agents like metoclopramide.	Pre-clinical studies	[40]
Cinchona bark *Procumbens cinchona* Pubescens	Warfarin	Possibly additive, potentiate warfarin's anticoagulant action.	Pre-clinical and clinical studies	[41]
Devils claw (Harpago-phytum)	Warfarin	additive effects to warfarin; i.e. blood thinning increases	Pre-clinical and clinical studies	[42]
Ephedra (*Ephedra sinica*)	Guanethidine, Ephedrine	Enhances a sympathomimetic effect of ephedra, Fatal Cardiac stimulation.	Clinical and preclinical Studies	[43]
Feverfew (*Tanacetum parthenium*)	Warfarin	Retards absorption.	Clinical and Preclinical Studies	[44]

Flaxseed oil (*Linum Usitatissimum*)	Insulin or oral hypo-glycaemic agents	Delays absorption of drugs taken simultaneously in diabetics delays	Pre-clinical and clinical studies	[45]
Garlic (*Allium Sativum*)	Warfarin	Additive effects (blood thinning increases) Potentiates warfarin's anticoagulant	Pre-clinical and clinical studies	[46]
Ginger (*Zingiber officinale*)	Warfarin	Additive effect; causes Immune Reconstitution Inflammatory Syndrome (iris), bleeding	Pre-clinical study and Case report	[47]
Ginkgo (*Ginkgo biloba*)	Aspirin	Increases the bleed clotting time, resulted in hyphema (pooling of blood inside the anterior chamber of the eye)	Clinical study	[48]
Ginseng (*Panax Ginseng*)	Phenelzine, triazolam, lorazepam	Headaches, tremors, insomnia, irritability, visual hallucinations	Clinical study and case report	[49]
Herbal sedatives Valerian (*Valeriana officinalis*)	Alcohol, antihistamines Phenytoin	Drowsiness, ability to use machinery; potentiates effects of antidepressants, anti-histaminic, antispasmodics	Clinical study	[50]
Ma-huang, *Mahuang (*Ephedra sinica*)*	MAO inhibitors cardiac glycosides or halothane, caffeine, procainamide, quinidine	causes arrhythmia i.e. irregular heartbeat therefore might cause serious side effects including heart	Pre-clinical study	[51]
Papaya extract (*Carica papaya*)	Warfarin	Papain increased INR, damages mucous membranes of GI tract. Additive effect to warfarin	Pre-clinical and clinical studies	[48]
Pineapple enzyme (*Ananas comosus*)	Bromelian	Diarrhea, increased tendency for bleeding if used simultaneously with anticoagulants and inhibitors of thrombocytic aggregation due to modulation of the arachidonate cascade	Pre-clinical and clinical studies	[42]
Psyllium seed (*Plantago* spp)	Coumarin derivatives, e.g. warfarin	Potentiates the effect of coumarin may cause bleeding	Pre-clinical studies	[47]
Shankha-phuspi (*Centella asiatica*, *Convolvulus pluricaulis*, *Nardostachys jaatamansi*, *Nepteta elliptica, Nepeta hindostana and Onsosma bracteatum*)	Alcohol, antihistamines. Phenytoin	Reduces plasma levels of phenytoin; seizure control lost	Clinical studies	[51]

4. CONCLUSION

The large increase in use of herbal medicine has led to increased concerns. Herbal medicines are comparatively safe when ingredients are pure and, prescribed appropriately. Life-threatening events reported from them are rare, compared to pharmaceutical products. However, there are always risks when appropriate regulations do not mandate the appropriate formulation of the remedies, or when self-medication fosters abuse. Researchers have given some basic rules for herb use guidelines:

- Be informed; seek out unbiased, scientific sources.
- Do not depend upon product claims alone.
- Inform your physician of self-medication regimens.
- Read labels carefully, know the benefits and risks and potential side effects.
- Know potential drug interactions.
- Never use if pregnant or nursing.
- Take care when giving to children or the elderly.
- Do not use for serious illnesses or for prolonged periods

Concomitant use of herbs and conventional drugs may present with untoward events. Evidence available in literature indicates various mechanisms through which this can occur. By interacting with conventional medication, herbal remedies may precipitate manifestations of toxicity or in the other extreme, therapeutic failure. A good knowledge of the potential of commonly consumed herbal medicines to interact with prescription medicines, irrespective of the nature of evidence available, will equip health professionals in their practice. Apart from those demonstrated in significant number of human subjects, not all reported HDIs are clinically significant. As such, more clinically relevant research in this area is necessary. This review provides information on commonly used herbs and their potentials for HDI and toxocity within the levels of evidence currently available.

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