World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

On review on herbal drug and drug interactions

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World Journal of Biology Pharmacy and Health Sciences, 2024, 20(01), 423–436

Publication history: Received on 05 September 2024; revised on 13 October 2024; accepted on 15 October 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.20.1.0782

Abstract

Herbal drugs are defined as any form of a plant or plant product that contains a single herb or combinations of herbs that are believed to have complementary effects. Although they are considered to be safe, because they are natural, they may have various adverse effects, and may interact with other herbal products or conventional drugs. These interactions are especially important for drugs with narrow therapeutic indices. Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include: bleeding when warfarin is combined with ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*), or danshen (*Salvia miltiorrhiza*); mild serotonin syndrome in patients who mix St John's wort (Hypericum perforatum) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of maniain depressed patients who mix antidepressants and Panax ginseng; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (Areca catechu); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (Pausinystalia yohimbe); potentiation of oral and topical corticosteroids by liquorice (Glycyrrhiza glabra); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-saiko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [Cassia senna] and cascara [Rhamnus purshiana]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs.

Keywords: Herbs; Herbal drugs; Side effects; Ginger; Garlic; Ginkgo biloba; Ephedra; Herbal drug interactions

1. Introduction

Herbs (herbal drugs) are generally defined as any form of a plant or plant product, including leaves, flowers, stems, roots and seeds, and they may contain a single herb or combinations of several different herbs that are believed to have complementary effects.[1]Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb drug interactions are limited, case reports scarce, and case series rare. This lack of data is also true of drug and drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended 7effects is not ethical). The true prevalence of drug interactions is substantial but unknown. Herbs or herbal products have been used since the dawn of the humanity and improve health, and according to The World Health Organization (WHO) an estimated 80 percent of the world's population presently uses herbal medicines for some aspect of primary health care. They are also commonly used by patients with certain chronic medical conditions including breast cancer, human immunodeficiency virus (HIV), asthma and rheumatological disorders.[2,3] Although there are few reliable estimates of the prevalence in use of herbal medicines (HM), the market for HM continues to expand rapidly and has grown into a multibillion-dollar industry across the world .[4,5]

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The use of herbal medicines (HM) is on the rise among the global population. Although the safety profile of many herbal medicines is promising, accumulated data show evidence of significant interactions with medications, which can place individual patients at great risk. A range of electronic databases have been reviewed for articles published in this field: Medline, Allied and Complementary Medicine Database, Health STAR, AMBASE, CINHAL, Cochrane Library, as well as Internet documents and manually searched references in medical journals. In this review, we examined the literature from 1966 to 2006 and focused on the importance of the risk of drug interactions and potential side effects when HM are involved. We discuss these in light of the documented findings.

HM chemical constituents responsible for pharmacological activity are many and complex, and the majority of them have not been identified. Distribution of constituents is not uniform throughout a plant. So, depending on the plant part used medicinally, chemical constituents could vary both qualitatively and quantitatively. For the same plant part, constituents vary in relation to other factors such as intraspecies and interspecies variation in components, climate, harvesting, drying, storage and transport conditions, preparation method and method of extraction. The purpose of this review, the term HM means unconventional or alternative therapies and includes herbs, herbal materials, herbal preparations supplied by herbalists, and finished or manufactured herbal products found in pharmaceutical dosage forms (tablets, capsules), as defined by the World Health Organization.[6] Main reason for their preference over the pharmaceutical drugs is that they are available without prescription and they are commonly assumed to be safe. Comparison of a National Health Survey made in 2002 in the United States with that made in 1997 revealed that there was a 50% increase in the use of herbal supplements, which meant that in the United States 38 million adults (20% of the population) were using these products and also that the use of herbal supplements in the USA is growing steadily by approximately 20% per year. [7,8-9,10]

1.1. Causes for herbal drug and drug interactions

- Herbs Containing constituents that induce liver enzymes might be expected to affect drug metabolism or elimination.
- How medications can change the way certain enzymes (proteins) works in body.
- Pharmacokinetics and pharmacodynamics, potentiality and incidences of adverse reactions like herb-drug interactions are unknown or have little information.
- Lack of evidences pertaining to the studies, dose and route of administration of herbs, herbal formulations and herbal drugs.
- Lack of standardization, and issues like difficulty in authentication of species, substitutes, adulteration and presence of contaminants.
- General human perceptions that product of herbal origin, herbal drug and their supplements are usually safe.

Objectives

To discuss the safety of intake of herbal medicines along with contemporary medicines in management of lifestyle disorders. Herbal drug and drug interactions affects either the pharmacokinetics fates or pharmacodynamics activities of drugs, leading to therapeutic failure and toxicities.

2. Material and methods

A simple validated high performance liquid chromatography method was developed for the evaluation of the effect of three kinds of active ingredients in traditional Chinese medicine (TCM) on the pharmacokinetics of glycyrrhetinic acid (GA),a kind of active component from the most commonly used TCM licorice. Our results revealed that all of the calibration curves displayed good linearity. Intra- and inter-day precision for GA ranged from 2.54 to 3.98% and from 4.95 to 7.08%, respectively. The recovery rates for GA were determined to be 96.3– 106.4%. All the samples showed satisfactory precision and accuracy in various stability tests. Plasma pharmacokinetic parameters including area under the concentration-time curve (AUC), elimination half-life ($t_{1/2}$), time to peak concentration (T_{max}) and peak concentration C_{max} were calculated. No significant difference was found as compared the groups administrating GA with and without other ingredients from TCM.

3. Results and discussion

Interaction of herbal products with other drugs will be the main topic of this review paper. Majority of suspected herbal drug interactions are identified through case reporting. All of the interactions with herbal products and conventional drugs are not known and even if it were, it would not have been possible to give them all in the context of a review

paper. Thus, in the present review, only interactions between some commonly used herbal products and conventional drugs will be considered. Herbal medicines are used to treat many different ailments, from common to serious and from acute to chronic,such as diabetes, hypertension, rheumatism, cancer, asthma and AIDS. Herb–drug interactions may occur in many situations, even when herbal medicines are used for weight reduction, performance and energy enhancement, or body building. An example is seen with the alkaloids obtained from species of Ephedra (Ephedraceae), administered as herbal medicines or as products containing synthetically prepared ephedrine and pseudoephedrine. The alkaloids, via catechol amines, can cause adverse cardiovascular events associated with arrhythmias, palpitations, tachycardia, myocardial infarction, and death.[11,12] Ephedrine raises blood pressure and induces peripheral vasoconstriction. Consumption of caffeine in Coffea arabica L. (Rubiaceae) or present in the same HM or in drugs, and in association with ephedrine, increases the cardiovascular risk.[13,14] The danger of using ephedrine containing products is higher in patients who are sensitive to the effects of sympathomimetic agents (ie, patients with hypertension, hyperthyroidism, diabetes mellitus, psychiatric conditions, glaucoma, prostate enlargement, seizure disorders, and cardiovascular.[15]

3.1. Ginger (zingiber officinale)

Ginger root has gained global popularity recently and is mentioned in traditional Ayurvedic and Chinese medical literature. Southeast Asian countries are the largest producers of this root. The name ginger originates from the ancient Sanskrit word srngaveram ("horn root"). The root originates from Zingiber officinale, a tropical plant with green-purple flowers and a fragrant stem known as a rhizome. Indians and Chinese are believed to have used this ginger as a tonic for thousands of years to treat illness.[16,17] This spice can lower blood pressure and has been shown to cause arrhythmia in a small number of cases. Increasing bile acid secretion can aggravate gallstone formation.[18] ginger can help reduce nausea during pregnancy but does not significantly reduce vomiting.[19]

Figure 1 Ginger (Z*ingiber officinale*) [1]

Ginger is a source of numerous antioxidants in reducing lipid oxidation and reactive oxygen species formation. Studies have shown that the active components of ginger root are used to scavenge superoxide anion and hydroxyl radicals and inhibit lipid peroxidation in vivo.Current studies demonstrate the ability of 6-gingerols to suppress hyperproliferation and inflammatory processes leading to carcinogenesis, angiogenesis, and metastasis. Ginger is effective against gastrointestinal cancers such as gastric, cholangiocarcinoma, liver, pancreatic, and colorectal cancers.[20,21,22,23]

Ginger can increase the anticoagulant effect of warfarin, possibly leading to warfarin toxicity and bleeding.[24]

Ginger may inhibit platelet aggregation. Consequently, ginger should be used with caution in patients prescribed antiplatelet medications to avoid an increased risk of bleeding.[25]

Ginger can increase the risk of hypoglycemia; therefore, it should be used with caution in patients prescribed oral hypoglycemic agents.[26]

3.2. Garlic

Garlic (Allium sativum L.; Family: Amaryllidaceae) is an aromatic herbaceous annual spice and one of the oldest authenticated and most important herbs that have been used from ancient times as traditional medicine.[27,28] Allium species and their active components are reported to reduce the risk of diabetes and cardiovascular diseases, protect against infections by activating the immune system and have antimicrobial, antifungal, anti-aging as well as anti-cancer properties which confirmed by epidemiological data from human clinical studies.[29] Garlic is well-known to be used in food preparation, especially dried foods for storage and some types of soup and it can be utilized in both fresh and dehydrated states.[30]

- When taken by mouth: Garlic is likely safe for most people. Garlic has been used safely for up to 7 years. It can cause side effects such as bad breath, heartburn, gas, and diarrhea. These side effects are often worse with raw garlic. Garlic might also increase the risk of bleeding and cause allergic reactions in some people.
- When applied to the skin: Garlic products are possibly safe. Gels, pastes, and mouthwashes containing garlic have been used for up to 3 months. But garlic might cause skin damage that is similar to a burn. RAW garlic is possibly unsafe when applied to the skin. It might cause severe skin irritation. Although garlic is a healthy addition to a balanced diet, eating too much may cause several side effects. garlic has antithrombotic properties, meaning that it may prevent blood clots from forming.

3.3. Major Interaction

Do not take this combination

3.4. Saquinavir (Fortovase , Invirase interaction with Garlic).

Saquinavir is a medication taken for HIV. Garlic might decrease how much saquinavir goes into the blood. This might decrease the effects of saquinavir.

Moderate Interaction: Be caution with this combination.

Figure 2 Garlic (*Allium sativum*) [2]

3.5. Ginkgo (Ginkgo biloba)

Ginkgo (Ginkgo biloba leaves) is accepted as a vasodilator and an antiplatelet product and is used mainly for memory deficits, for the treatment of dementia, vertigo, peripheral vascular diseases and tinnitus. [31,32,33,34] In terms of treatment for existing dementia, data has been contradictory regarding the efficacy of Ginkgo biloba extract (EGb). A 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of 309 patients in 1997 concluded that EGb was safe and though modestly, it appeared to stabilize and improve the cognitive performance as well as social functioning of dementia patients for six months to 1 year.[35] Ginkgo biloba extract has been shown to affect several neurotransmitter pathways and brain structures, mostly in animal studies. EGb761 limits stress-induced corticosterone hypersecretion by reducing the number of adrenal peripheral benzodiazepine receptors in rats.[36] In general, Ginkgo biloba is safe and well-tolerated. The maximum recommended dose for ginkgo extract is 240 mg/day.[37]

Figure 3 Ginkgo (*Ginkgo biloba*) [3]

Mild adverse effects include headache, heart palpitations, gastrointestinal upset, constipation, allergic skin reactions.[38] Raw ginkgo seeds contain potentially toxic cyanogenic glycosides.[39] Contact or ingestion of ginkgo's seed can be poisonous. It can cause a serious allergic skin reaction such as acute generalized exanthematous pustulosis and also convulsions.[40,41] As discussed in this review, bleeding, seizure, serotonin syndrome could be potential consequences of ginkgo toxicity. There is no antidote for ginkgo. Treatment includes discontinuation of ginkgo and appropriate symptom control depending on the manifestation of each toxication case. As discussed above, physicians should be aware of the increased risk of bleeding when Ginkgo biloba was co-administered with other agents that have potential to increase bleeding (NSAIDs, antiplatelet, anticoagulant therapies, garlic, ginger, ginseng, etc.)

3.6. Ginseng (panax Ginseng)

Ginseng is reported to be the fifth most commonly used herbal drug in the USA. Active components of different Ginsengs are different and thus wide variations exists among ginseng products. Asian (or Korean) ginseng (roots of Panax ginseng) is generally standardized to ginsenosides (a group of compounds known as steroidal saponins) and is used for various indications including erectile dysfunction, prevention of cancer, to enhance physical function, and improve cognitive functions; it is advertised as an immune system stimulant. In Chinese medicine it is also used for various cardiovascular diseases. [42,43]

Figure 4 Ginseng (P*anax ginseng*) [4]

Panax ginseng is likely safe when taken for up to 6 months. Panax ginseng is possibly unsafe when taken for more than 6 months. It might have some hormone-like effects that could be harmful when used long-term. The most common side effect is trouble sleeping. Uncommon side effects that have been reported include severe rash, liver damage, and severe allergic reactions. Panax ginseng has actions against inflammation, oxidative stress, mitochondrial dysfunction, and apoptosis. Ginsenosides are involved in neuroprotective effects due to anti-apoptotic, antioxidant, and anti-inflammatory effects Ginseng extract can decrease symptoms of fatigue, nausea, vomiting, and dyspnea in patients with

cancer Panax ginseng exert can act as a complementary treatment in managing patients with chronic diseases related to aging.

3.7. Valerian (Valeriana oficinalis)

Valerian is used as a sedative, especially in the treatment of insomnia and it is reported that almost all herbal sleep aids contain valerian.Historically, the sedative and hypnotic medication of (Valeriana officinalis)Valerian L. (Valerian) dates back to the first century AD. More than 200 valerian species spread over the world, among which, Valerian is the most well known in Europe and North America. Valerian is regulated by the US Food and Drug Administration (FDA) as a dietary supplement. According to the European Medicine Agency (EMA), the well-established oral administration of Valerian extract relieves nervous tension as well as sleep disorders (Shinjyo et al., 2020). A study shows that administration of Valerian extract (80 mg/kg) resulted in significant improvements in sleep latency time and total sleep time, exhibiting a sleep-promoting activity in a pentobarbital-induced model (Sung Hee Han et al., 2018). It has been reported the daily intake of Valerian/Lemon balm plant pair capsules improved sleep quality in women during menopause probably owing to the pain intervention of Valerian (Behboodi Moghadam et al., 2016). Valerian is considered relatively safe and well-tolerated except for mild gastrointestinal symptoms or headaches (Zare Elmi et al., 20221. The roots of valerian (valeriana officinalis) , a flowering plant has been widely used to treat sleeping disorders in Europe for decades.[44] ncarnata A case of a patient self-medicated with Valeriana officinalis L. and Passiflora i L. while he was on lorazepam treatment was reported. Handshaking, dizziness, throbbing.

Figure 5 Valerian (V*aleriana officinalis*) [5]

and muscular fatigue were observed within the 32 h and his medical history revealed a generalized anxiety disorder and medicinal plant consumption but no neurological disorder. It was proposed that the active principles of Valerian and passionflower might have increase the inhibitory activity of benzodiazepines binding to the GABA receptors, causing severe secondary effects. [45,46]

3.8. Ephedra (ma haung)

Herba (Ephedra), also known as “Ma Huang” in China, grows mostly in dry desert environments and has been used in traditional Chinese medicine for more than 5000 years.[47] The stems and seeds of Ephedra contain many antibacterial components [48] and the inhibitory effects and mechanisms of Ephedra on different types of bacteria are different. Phenolic compounds isolated from Ephedra have remarkable antibacterial activity against Gram-negative and -positive bacteria and fungi Ephedra. [49]. Ephedra may increase bleeding in sensitive individuals, such as those taking aspirin or other blood-thinning medications.

- Ephedra may interact with blood pressure lowering medications, particularly clonidine.
- Ephedra may interact with narcotics prescribed for pain, such as morphine and codeine; codein5 may also be prescribed for cough.
- Ephedra May interact with theophylline (used for asthma).

Ephedra can produce side effects, such as irritability, restlessness, anxiety, insomnia, headaches, nausea, vomiting, and urinary problems. More serious side effects include high

Figure 6 Ephedra (*Ma haung*) [6]

blood pressure, rapid or irregular heartbeat, stroke, seizures, addiction, and even death. If you experience any of these adverse effects, discontinue using ephedra and contact your provider immediately. While no specific interactions (positive or negative) between the herb ephedra and conventional medications have been reported, the active ingredients of ephedra, ephedrine, and pseudoephedrine have been associated with several serious drug interactions. We may assume, for safety's sake, that drugs that interact with ephedra's active ingredients may also interact with the herb ephedra.

3.9. St. John's Wort (SJW) (Hypericum perforatum):

St. John's Wort is a very popular antianxiety and antidepressant product. It has also been reported to block metastases and act against inflammation and lung fibrosis.

Although SJW has a good safety profile, it can undergo both pharmacokinetic and pharmacodynamic interactions with many other drugs.[50,51,52] Well-documented SJW interactions include reduced blood cyclosporin concentration, as suggested by multiple case reports as well as by clinical trials, serotonin syndrome or lethargy when SJW was given with serotonin reuptake inhibitors, unwanted pregnancies in women while using oral contraceptives and SJW, and reduced plasma drug concentration of antiretroviral (e.g., indinavir, nevirapine) and anticancer (i.e., irinotecan, imatinib) drugs. Hyperforin, which is believed to contribute to the antidepressant action of St John's wort, is also strongly suspected to be responsible of most of the described interactions.

Herbal product annual retail sales reflect the growing consumer interest; indeed, sale statistics demonstrate a 3.4% increase from 2003 to 2004 and an additional 2.1% increase in 2005 compared to 2004 for all herbal products[53] The reason of this wide usage of natural drugs is the notion that, being natural, all herbs are safe. However, contrary to popular belief that "natural is safe", herbal drugs can cause significant side effects, including herb–drug interactions.[54,55] The effect of SJW on P-glycoprotein or CYP enzymes is generally observed after long treatment [ten or more days [,56,57,58]; data with treatment for lesser numbers of days (i.e., 4–9 days) are not available] with studies reporting no effect (or even nonclinically relevant stimulating effects) following acute (1–3 days) SJW administration. [59,60] Effects on CYP or P- glycoprotein after SJW treatment in the 4–9-day range are not available. In addition, the extent of CYP3A4 and P-glycoprotein induction was found to be comparable among a number of ethnic groups, namely Caucasians, Africans, Americans, Hispanics, Chinese, Indians, and Malays.[61]

SJW has been shown to clinically interact with a number of drugs (Tables II and III), including immunosuppressants, contraceptives, cardiovascular, anti-HIV and anticancer drugs, anxiolytics, antidepressants, anticonvulsants, anesthetics, drugs used in addicted patients (e.g., methadone), muscle relaxing agents, drugs acting on the respiratory system, hypoglycemic, antimicrobic, and antimigraine medicines as well as drugs acting on the gastrointestinal tract. These interactions are discussed below.

3.10. Which medicines interact with St.John's Wort

The table below lists medicines for which there is varying degrees of evidence of a possible interaction with St John's wort. For some (e.g. cyclosporin, warfarin, indinavir, carbamazepine) the loss of clinical effectiveness is potentially serious. The table gives an indication of the nature and strength of the evidence of interaction, describes the effect of an

interaction should it occur, and provides advice on the management of patients. For some of the medicines listed there is at present no more than a theoretical possibility of interaction.[62,63]

The table is not exhaustive, but it covers the information available to date. Other medicines not included in this list therefore may also interact with St John's wort preparations. In general, the following medicines are not likely to interact with St John's wort preparations:

- topical medicines with limited systemic absorption (inhalers, skin creams and ointments, eye and ear drops, enemas etc.)
- non-psychotropic medicines which are principally renally excreted

St John's wort (SJW) extracts, prepared from the aerial parts of Hypericum perforatum, contain numerous pharmacologically active ingredients, including naphthodianthrones (e.g., hypericin and its derivatives), phloroglucinols derivatives (e.g., hyperforin, which inhibits the reuptake of a number of neurotransmitters, including serotonin), and flavonoids. Such extracts are widely used for the treatment of mild-to-moderate depression.

Figure 7 St John's wort (*Hypericum perforatum*) [7]

3.11. Cranberry (vaccinium macrocarpons)

Cranberry (Vaccinium macrocarpon) is an evergreen shrub that grows in bogs in North America. It produces dark red fruits that contain salicylic acid. Chemicals in cranberries keep bacteria from sticking to the cells in the urinary tract. But they don't seem to be able to remove bacteria that are already stuck to these cells. This might explain why cranberry helps prevent urinary tract infections (UTIs), but doesn't help treat them.

Cranberry juice is a popular beverage with many health benefits. It has anthocyanins to supplement dietary needs. Based on in vitro evidence cranberry juice is an inhibitor of CYP enzymes and at higher amounts as potent as ketoconazole (CYP3A) and fluconazole (CYP2C9).[64] A patient who was on warfarin therapy experienced an increase in INR on 2 different occasions after consuming cranberry juice for a few days. Thus, we suggest that people who are treated with anticoagulants or who take antithrombotic agents should be aware that consumption of large quantities of cranberry may result in an unwanted interaction, increasing the bleeding time.

When taken by mouth: Cranberry is commonly consumed in foods. Cranberry juice and cranberry extracts are likely safe for most adults. Drinking too much cranberry juice might cause some side effects such as mild stomach upset and diarrhea in some people

Figure 8 Cranberry (*Vaccinium macrocarpons*) [8]

3.12. Liquorice (Glycyrrhiza glabra)

Licorice is an herb that grows in parts of Europe and Asia. Licorice root contains glycyrrhizin, which can cause side effects when eaten in large amounts.

The chemicals in licorice are thought to decrease swelling, decrease cough, and increase the chemicals in our body that heal ulcers. Many "licorice" products made in the U.S. actually don't contain licorice. They contain anise oil, which has the smell and taste of "black licorice".

Licorice, the roots and rhizomes of Glycyrrhiza glabra L., has been used as a medicinal herb, herbal adjuvant, and flavoring agent since ancient times.[64] Recently, licorice extracts have become popular as dietary supplements used by females to alleviate menopausal symptoms. Exposure to licorice products containing high levels of glycyrrhizic acid can cause hypokalemia, but independent from this effect, preclinical data indicate that licorice can inhibit certain cytochrome P450 (P450) enzymes. [65]

Generally-recognized-as-safe status, the licorice species Glycyrrhiza glabra has been associated with some toxicity. Preclinical studies suggest that G. glabra might cause pharmacokinetic drug interactions by inhibiting several cytochrome P450 enzymes. This phase 1 clinical study addressed these concerns by evaluating clinically relevant effects with respect to CYP3A4/5, CYP2C9, CYP2D6, and CYP1A2. These results showed that a standardized G. glabra extract did not cause any clinically relevant pharmacokinetic drug interactions with four major cytochrome P450 enzymes.[66] Licorice that contains glycyrrhizin is possibly unsafe when consumed in large amounts or for a long time. Eating licorice 5 grams or more daily for several weeks can cause severe side effects including heart attack. People who have heart disease, kidney disease, or high blood pressure are more sensitive to it. Ingesting large amounts of licorice from candy, lozenges, or tea might also cause serious side effects.

Figure 9 Liquorice (*Glycyrrhiza glabra*)

3.13. Moderate Interaction

Be caution with this combination

3.14. Digoxin (Lanoxin) interacts with liquorice

Large amount of liquorice can decrease potassium level in the body. Low potassium levels can increase the side effects of digoxin.

3.15. Estrogens interact with liquorice

Licorice seems to change hormone levels in the body. Taking licorice along with estrogen might decrease the effects of estrogen.

Liquorice is a constituent in many of home remedies for cough and sore throat. The active constituent glycyrrhizin causes hypokalaemia and sodium retention (Walker and Edwards, 1994) and may result in hypertension, pulmonary edema and cardiomyopathy (Walker and Edwards, 1994; Hasegawa et al., 1998). Prolonged use may cause irregular heartbeats and muscle weakness. Prolonged use of liquorice along with cardiac glycosides may cause cardiactoxicity (Cheng, 2000).

3.16. Kava-kava (Piper methysticum)

Kava (Piper methysticum) is a South Pacific psychotropic plant medicine that has anxiolytic activity. This effect is achieved from modulation of GABA activity via alteration of lipid membrane structure and sodium channel function, monoamine oxidase B inhibition, and noradrenaline and dopamine re-uptake inhibition.[67] Kava is available over the counter in jurisdictions such as the USA, Australia and New Zealand. Due to this, a review of efficacy, safety and clinical recommendations is advised.[68]

Figure 10 kava-kava (*Piper methysticum*) [10]

Kava might cause sleepiness and slowed breathing. Some medications, called sedatives, can also cause sleepiness and slowed breathing. Taking kava with sedative medications might cause breathing problems and/or too much sleepiness.[69]

When taken by mouth: Kava is possibly safe when taken for up to 6 months. Using kava can make it difficult to drive or operate machinery safely. Do not take kava before you plan on driving. "Driving-under-the-influence" citations have been issued to people driving erratically after drinking large amounts of kava tea.[70]

People might have heard that using kava can cause liver damage. This seems to be rare and is most often linked to long-term use of very high doses. Most people who have used kava haven't experienced liver toxicity. Also, past cases of liver toxicity might not be due to kava. Other factors may have contributed to these toxic effects.[71]

During the past few decades, kava has also gained popularity in Western countries as well, due to its anxiolytic and sedative properties. However, in recent years, kava has been implicated in several liver failure cases which led to its ban in many countries and this has prompted wide discussion on its relative benefits and risks as a social beverage and a herbal remedy. Recently, it has been shown that several kavalactones, the assumed active principles of kava extracts, are potent inhibitors of several enzymes of the CYP 450 system (CYP1A2, 2C9, 2C19, 2D6, 3A4 and 4A9/11). [72] This

indicates that kava has a high potential for causing pharmacokinetic drug interactions with other herbal products or drugs, which are metabolised by the CYP 450 enzymes.

4. Conclusion

It is evident from the data given above that due to a worldwide rise in the use of dietary supplements and/or herbal preparations, the incidence and severity of herb- drug interactions are increasing. This poses a serious problem in the treatment of patients, and represents a serious and under-recognized hazard in clinical care, especaially for those using drugs with narrow therapeutic indices. More clinical data regarding herb drug pharmacokinetic and/or pharmacodynamic interactions are needed to make informed decisions regarding patient safety. However, we should be very careful when interpreting the literature data since the findings from in vitro studies or animal studies do not always correlate with the situation in the clinic, or minor effects observed in clinical studies do not have to be clinically relevant.

Efficacy and safety of herbal products should be obtained by well-designed clinical trials, pre-marketing approval regarding safety and strict post-marketing surveillance.

It has been projected that the possibility of drug interactions increase almost exponentially with the number of drugs used. Drug interactions may cause either adverse effects or sometimes therapeutic failure. It is desirable to understand the basic pharmacology of drugs so as to avoid giving drugs that are additive in nature or those acting on the same or multiple sites as well as to remember the important inducers of metabolism. The prescriber and also the patient should take care while taking any OTC, natural products and food during the medication. The use of herbal drugs along with prescribed contemporary medicines is escalating in both developed and developing countries, with or without the knowledge of herbal remedies resulting in potential herb-drug interactions. This can be avoided by bringing effective changes in healthcare curriculum, positive response from the accreditation agencies, by proper implementation of the acts like Drugs and Cosmetics Act, Consumer Protection Act, with necessary amendments. Crude drugs and finished herbal products are often marketed as herbal medicines or dietary supplements for their claimed therapeutic effects and miraculous cures. Unfortu-neatly, HM are not free of risk and interactions between these products and prescription medications are an increasing concern and may have significant public consequences. However, in most cases the claims have not been substantiated and few HM have been subjected to double-blind, randomized, placebo-controlled clinical trials. Their potential to cause adverse effects and interaction with conventional drugs are an understudied field of research. It is important to be aware that most HM fall outside of the regulatory framework and evidences is generally lacking on their safety, efficacy or standards of manufacture.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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