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Herbal Drug Interactions – A Major Safety Concern

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ABSTRACT

Use of herbal medicinal products (HMPs) has several folds increased over the past few decades. Apart from the fact that HMPs are relatively economical and provide solution where other therapies do not, one of the major beliefs that HMPs are always safe is always been exploited by the manufacturers while promoting their products. But the increasing evidences about toxic effects of herbal formulations have drawn the attention of scientists all over the world. Among several factors, herbal drug interactions (HDI) are one of the major concerns. HDI can be caused by either pharmacodynamic or pharmacokinetic mechanisms. One important factor that increases the likelihood of having an herbal drug interaction is concomitant use of herbal with drugs that have a narrow therapeutic index such as digoxin, antiepileptic drugs, antineoplastic agents, immunosuppressant's, and warfarin. Most of the current evidence concerning interactions between natural products and drugs is based on known or suspected pharmacological activity, data derived from *in vitro* studies etc. Since HDI can be fatal most of the times, there should be proper regulation on the labeling of herbals to prevent such interactions and to ensure safe use of herbals.

INTRODUCTION

When a drug is taken with another substance leads to a drug interaction- prescription drugs, over-the-counter drugs, alcohol, herbs, supplements, food, water etc. There are various kinds of potential interactions that have the possibility of either increasing or decreasing drug concentrations in the body that could lead to the development of drug resistance. It could also cause the drugs to be ineffective to treat the condition because the blood levels are too low, or trigger an overdose because the drug concentrations are too high. In case of some drug interactions death may also occur^[1]. The general public's use of herbals has increased over the past 10 years. Aside from the need to appraise these products for safety and efficacy, health care providers and the public need to know whether interactions might occur when these products are used in combination with conventional drugs. Most of the current evidence concerning interactions between natural products and drugs is based on known or suspected pharmacologic activity, data derived from *in vitro* studies, or anecdotal case reports that frequently lack pertinent information. The relevance of such information in terms of severity and outcome is questionable. More recently, there have been some reliable, documented case reports, *in vivo* studies, and clinical trials that have evaluated herbal-drug interactions. Results have sometimes been contradictory, and much more research is needed. The purpose of this article is to provide an evidence-based discussion and information to educate patients about potential herbal-drug interactions^[2].

DRUG INTERACTION RISK FACTORS

Most of people have the mistaken belief that being natural, all herbs and foods are safe. It could not be said that is true perspective. Constantly, herbs and foods may interact with medications normally taken that result in serious side reactions. Experts suggest that natural does not mean it is completely safe. The medication that is taken by mouth travels through the digestive system in the same way as food and herbs taken orally do. When drugs and certain foods are taken at the same time,

they might interact in such a way that decrease the effectiveness of the ingested drug or reduce the absorption of food nutrients. High-risk patients, such as the elderly patients taking three or more medications for chronic conditions, patients suffering from diabetes, hypertension, depression, high cholesterol or congestive heart failure should be especially monitored for such drug food interactions. Insufficient nutritional status can impair drug metabolism. Some people at higher risk for drug-nutrient interactions They are who ^[3]:

- have impaired hepatic, renal or gastro-intestinal function,
- are nutritionally compromised due to chronic disease,
- have recent weight loss or dehydration,
- Are on multiple and prolonged drug therapy are at the extremes of age with changes in lean body mass, total body fluids and plasma protein concentration ^[4].

WHY PEOPLE USE HERBAL MEDICINES

Herbal medicines are being used by 75-80% of world population especially those living in developing countries ^[5]. It has been reported that most plants and plant extracts are used as prescribed medicines in France and Germany ^[6]. The number of medicals tending to use such herbal medicines is increasing, those suffering from cancer are inclined to use herbal medicine due to hope to cure, disease improvement, preventing disease to convert to metastatic form, supporting immunity system, reducing stress, and relaxation. Furthermore, the main aims of using herbal medicine in Cancer treatment are: Primary prevention of cancer through creating an unfavorable environment for growth of cancer cells, Prevention of a recurrence of cancer, Increasing body's immune system, and reducing side effects resulting from using modern treatment methods including chemotherapy and radiotherapy ^[7].

Difference of herbal drugs and chemical drugs: In spite of similarities, there are some important differences between modern and herbal medicines. It is claimed that various parts of plant extract work together in a synergetic way. The evidence show that synergetic and buffering effects of whole plant extracts. But that these characteristics apply for all plants is still under question. Synergetic and buffering principles are applied for combination of different plants. It was reported that the combination of plants increases therapeutic effects and reduces side effects. This is in contrast with using methods of usual and chemical medicines, because using several modern drugs at the same time is avoided as much as possible ^[8]. Herbal medicines are sophisticated natural compounds influencing at the same time the different phases of diseases through different mechanisms. On the other hand, chemical medicines are individual synthetic compounds interfering in an ideal ^[9].

PROBLEMS SPECIFIC TO HERBAL PRODUCTS

Quality

The quality of herbs is very important as some herbs require specialist treatment after collection, for example the most highly esteemed quality of Asian ginseng comes from plants of certain varieties that are at least 7 years old, and which have been fermented and dried before processing. This makes them expensive and thus very liable to adulteration, the most common adulterant being liquorice, which has known adverse reactions, including an interaction profile different to that of ginseng. Mistaken identity and adulteration may account for inaccurate reports as to the safety of an herbal medicine and damages the reputation of a herb. Even more dangerous is the practice of adulteration of herbal medicinal products with synthetic medicines, such as corticosteroids and even warfarin ^[10]. Quality control and good manufacturing practice is therefore obviously of equal importance to herbal medicines as to conventional drugs, and when quality control methods can be further refined, H-DI reports will become more reliable. At present it is difficult to decide whether there is a true interaction or not, since the composition (and even the identity) of a herb within a herbal product cannot always be validated. Even though reputable herbal manufacturers have quality assurance procedures in place, which minimise variability within their own products, there will inevitably be differences between preparations made by different methods and by different companies ^[11].

Complexity and Variability

Herbal medicinal products are by definition complex mixtures of many compounds, leading to the possibility of a total extract having a different profile of H-DIs than an isolated compound. For example, genistein inhibits various CYP enzymes but the whole extract of soya, in which genistein occurs, does not ^[12]. Opposing effects have even been reported on the extracts of the same plant using *in vitro* and *in vivo* methods: in a study looking at the effect of a liquorice extract on CYP 3A4 using a microtitre plate assay of enzyme activity, inhibition was found ^[13], whereas the extract was reported to increase activity of the CYP3A family, and also of CYP1A2 and CYP2B1, after repeated dosing in rodents ^[12]. It is not known whether this is due to the extracts having a different composition, or whether it is a species specific effect, or perhaps it is an example of the difference between *in vitro* and *in vivo* results. This phenomenon illustrates once again the danger of extrapolating the results of *in vitro* or *in vivo* experiments, which examine the experimental effect of a single compound, on a possibly species specific enzyme, in a laboratory, to clinical situations. It is therefore most important that the association between experimental results and clinical situations is clarified to enable accurate predictions to be made, and that the contribution of a single ingredient in a mixture is put in perspective ^[14].

The constitution of a herbal medicinal product can also vary greatly, depending on the source material, which is determined by genetics, and the conditions under which it is grown, as well as the method of processing, including extraction, storage, and formulation of the product.

TYPES OF INTERACTIONS

Food and Drug Interactions

These may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances. Interactions between food and drugs may inadvertently reduce or increase the drug effect. Some commonly used herbs; fruits as well as alcohol may cause failure of the therapy up a point of to serious alterations of the patient's health. The majority of clinically relevant food-drug interactions are caused by food induced changes in the bioavailability of the drug^[15]. There are three types of accepted drug-food interactions based on their nature and mechanisms.

- Type I interactions affect absorption. They cause either an increase or decrease in the oral bioavailability of a drug. The precipitant agent may modify the function of enzymes or transport mechanisms that are responsible for biotransformation.
- Type II interactions affect the systemic or physiologic disposition and occur after the drug or the nutritional element has been absorbed from the gastrointestinal tract and entered the systemic circulation. Changes in the cellular or tissue distribution, systemic transport, or penetration to specific organs or tissues can occur.
- Type III interactions refer to the elimination or clearance of drugs or nutrients, which may involve the antagonism, impairment or modulation of renal and/or enterohepatic elimination^[16].

Herb and Drug Interaction

In the last two decades there has been a considerable increase in the herbal remedy market. Interactions between herbal remedies and drugs have been put on the agenda and received increased attention^[17]. Both serious and less serious adverse interactions have been reported e.g. between the drug cyclosporine and St. John's wort (*Hypericum perforatum*), and between drugs like warfarin or aspirin which are reported to interact with a range of herbs like garlic (*Allium sativum*), cranberry (*Vaccinium oxycoccos*), Ginkgo Biloba, ginger (*Zingiber officinale*) and grape fruit (*Citrus paradisi*). Co-use of herbs and drugs might alter the drug's pharmacokinetics and/or pharmacodynamics, hence causing unexpected adverse effects of the drug^[18]. Studies have reported extensive use (40-56%) of herbs in the general population. The 2007 National Health Interview Survey, USA, reported that nearly 20% of the general populations were using herbs^[19]. The typical herb user was female, aged 30 to 69 years, with higher education or hospitalized in the last year. Forty-one per cent of USA adults reported the use of herbal remedies to self-treat before seeking medical care from a physician^[20].

Examples of Various Herb - Drug Interactions

An interaction may involve having the herb component to cause an increase/ decrease in the amount of drug in the blood stream. Drug-herb interactions are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions.

Ginkgo biloba and Warfarin: Ginkgo biloba may also interact with warfarin (Coumadin). A 78-year-old woman who had been taking warfarin for five years after coronary bypass surgery suffered a left parietal hemorrhage after using a ginkgo product for two months. No change was noted in her prothrombin time. The intracerebral bleeding was attributed to the antiplatelet effects of ginkgo^[21].

Ginseng and anti-clotting agents: Ginseng may cause decreased effectiveness of certain anti-clotting medications. Persons using ginseng see increased heart rate or high blood pressure. It may cause bleeding in women after menopause^[22].

St. John's wort–drug interactions: Immunosuppressant's such as cyclosporine and oral contraceptives usually interact with St. John's wort, it decreases the efficacy of oral contraceptives. The current available evidence suggests that all herbal medicines should be discontinued two weeks prior to surgery to avoid any complications^[23].

Garlic with antiplatelet agents: Garlic is very commonly used for carminative and thermogenic properties. Interaction between garlic and antiplatelet is a moderate type of herbal - drug interaction. When garlic is taken with antiplatelet agents increases the risk of bleeding and may be fatal to the patient^[24].

Ginger and anticoagulants: Ginger is primarily used to treat nausea, but it is also used as an anti-inflammatory, a pain remedy, a warming remedy and a cholesterol-lowering herb. Although severe interaction of ginger with any drug has not been reported but some herbalists recommend avoiding use by patients taking anticoagulant medications; no adverse interactions have been reported^[25].

Licorice and immunosuppressant's: Immunosuppressant's are the agents which are used to suppress immunity of human beings in case of autoimmune disorders. Immunostimulant effect of licorice herb may offset immunosuppressant effects of drug taken with it and may reduce immunosuppressant levels^[26].

Grapefruit juice – Drug interactions: Foods are intended to be safe for human consumption but there are few foods which show interactions with the drugs when taken along with them. Grapefruit juice shows interaction with around 20 drugs by increasing their oral bioavailability. It interacts with lovastatin drug which is an antilipidemic agent by irreversible inhibition of the enzyme cytochrome oxidase [27].

CONCLUSION

Contrary to popular belief that “natural drugs are safe”, herbal medicines can cause significant toxic effects, drug interaction and even incidences of morbidity or mortality. This article is not against herbal medicines. Based on evidence from *in vitro*, *in vivo* and clinical studies, herbal and other dietary supplements have shown interaction with many drugs. Still many drug-herbal interactions are difficult to evaluate. Physicians must indulge in patient counseling to avoid risks of drug interaction with herbal supplements. The interaction often involves drug-metabolizing enzymes and drug transporter systems, besides pharmacodynamic interaction. Since the pharmacokinetic and pharmacodynamic characteristics of most herbal and other dietary supplements are not completely recognized, potential interactions are often not predictable. Potential interactions are likely to occur with drugs with narrow therapeutic index. The evidence-based evaluation used in the study can be used to evaluate reliability of the case reports.

REFERENCES

1. Ismail M, Yaheya M. Drug food interactions and role of a pharmacist. *Asian Journal of Pharmaceutical and Clinical Research*. 2009; 4(2):50-55.
2. Linda SS, Karen JM. Herbal – Drug interactions. *Inet Continuing Education Journal*. 2005; 9(10):40-45.
3. Zyl VM. The effects of drugs on nutrition. *South African Journal of Clinical Nutrition*. 2011; 24(3):38-41.
4. Otles S, Senturk A. Food and drug interactions – A general review. *Acta Scientiarum Polonorum Technologia Alimentaria*. 2014 13(1): 89-95.
5. De Araujo Junior RF, De Souza TP, Pires JG, Soares LA, De Araujo AA, et al. A dry extract of *Phyllanthus niruri* protects normal cells and induces apoptosis in human liver carcinoma cells. *Experimental Biology and Medicine*. 2012; 237(11):1281-1284.
6. Mukherjee AK, Basu S, Sarkar N, Ghosh AC. Advances in cancer therapy with plant based natural products. *Current Medicinal Chemistry*. 2001; 8(12):1467-70.
7. Tavakoli J, Miar S, Zadehzare MM, Akbari H. Evaluation of Effectiveness of Herbal Medication in Cancer Care: A Review Study. *Iranian Journal of Cancer Prevention* 2012; 5(3):144-48.
8. Pal SK, Shukla Y. Herbal medicine: current status and the future. *Asian Pacific Journal of Cancer Prevention* 2003; 4(4):281-85.
9. Safarzadeh E, Sandoghchian. Herbal medicine as inducers of apoptosis in cancer treatment. *Advanced Pharmaceutical Bulletin*. 2014; 4(1): 421-25.
10. Williamson EM. Interactions between herbal and conventional medicines. *Expert Opinion in Drug Safety* 2005; 26(15):1075-1092.
11. Loew D, Kaskin M. Approaching the problem of bioequivalence of herbal medicinal products. *Phytother Res*. 2002; 16(8):705-712.
12. Zhou S, Gao Y, Huang M, Xu A, Paxton JW. Interactions of herbs with cytochrome P450. *Drug Metab Rev*. 2003; 35(1):35-98.
13. Budzinski JW, Foster BC, Vandenhoeak S, Arnason JT. An *in vitro* evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. *Phytomed*. 2000; 7(4):273-282.
14. Butterweck V, Darenfort H, Gaus W, Narstedt A, Schulz V, et al. Pharmacokinetic herb-drug interactions: are preventative screenings necessary and appropriate? *Planta Med*. 2004; 70: 784-791
15. Bushara R. Food and drug interactions. *Oman Medical Journal*. 2011; 26(2): 77-83.
16. Frago LR, Esparza JR. Fruits/ Vegetables drug interactions: Effects on drug metabolizing enzymes and drug transporters.
17. Van den Berg SJ. Safety assessment of plant food supplements. *Food and Function Journal*. 2011; 2: 760-65.
18. Woodward KN. The potential impact of the use of homeopathic and herbal remedies on monitoring the safety of prescription products. *Human and Experimental Toxicology*. 2005; 24: 219-225.
19. Complementary and Alternative medicine use among adults and children. United States – A survey, 2007.
20. The co-use of conventional drugs and herbs among patients in Norwegian general practice. 2013; 13:295-297.
21. Davis M. Herbal Remedies: Adverse effects and drug interactions. *Essential Tremor (ET)*.

22. Dharmananda S. Checking for possible herb – drug interactions. Director, Institute of Traditional Medicine, Portland.
23. Chavez ML, Chavez PI. Evidence based drug – herbal interactions. Bimedical Sciences Program. 2005; 3: 15-18.
24. Graham RE, Gandhi TK. Risk of concurrent use of prescription drugs with herbal and dietary supplements in ambulatory care.
25. Kemper KJ. Ginger (*Zingiber Officinale*). The Centre for Holistic Pediatric Education and Research.
26. Staines SP. Herbal Medicines: Adverse effects and drug – herb interactions. Clinical Pharmacy.
27. Singh I, Bhutani KK. Interaction of herbs and food products with drugs - Grapefruit juice as an example. National Institute of Pharmaceutical Education and Research. 2005; 4: 15-20.