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Effect of Concurrent Administration of Herbs on the Pharmacokinetics of Drugs: A Review

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Abstract

Herbal medicines are currently in high demand, and their popularity is steadily increasing as an alternative medicine. This is as a result of their perceived effectiveness, fewer side effects and relatively low cost. They are being used simultaneously with therapeutic drugs for the treatment and management of numerous medical conditions, but due to the complex mixture of bioactive constituents they are capable of affecting the pharmacokinetics and pharmacodynamics of conventional drugs when administered concurrently. Of serious concern is the concurrent consumption of herbal products and conventional drugs. Herb–drug inter-action (HDI) is the single most important clinical consequence of this practice. Using a structured assessment procedure, the evidence of HDI presents with varying degree of clinical significance. While the potential for HDI for a number of herbal products is inferred from non-human studies, certain HDIs are well established through human studies and documented case reports. This herb-drug interactions (HDIs) may lead to modifications in plasma drug levels resulting in therapeutic failure of the drug or, alternatively, it may cause drug-induced toxicity. The main routes proposed for HDIs include cytochrome P450 (CYP450)-mediated inhibition or induction and transport and flow proteins. In our review, some herbal medicines used for the treatment of various diseases were highlighted and case reports of their pharmacokinetics and pharmacodynamics herb-drug interactions were analyzed. Therefore, this review can be a quick reference tool for physicians, pharmacists and other healthcare professionals involved in therapy, and counseling towards appropriate use of drugs to maximize clinical outcomes.

Keywords: Drugs; Herbs; Interactions; Toxicity; Herb-Drug Interactions; Concurrent Administration

Abbreviations: HDIs: Herb-Drug Interactions; DDI: Drug-Drug Interaction; DFIs: Drug-Food Interactions; CAM: Complementary or Alternate Medicine.

Introduction

The term 'Herbal products' commonly refers to all types of preparations obtained from herbs, spices, roots, stems, leaves and other non-botanical materials of natural origin. They can be used therapeutically as prescription or over-the-counter medicines or even as food [1]. Due to high prices and potential side effects of synthetic drugs, people rely more on herbal drugs and this trend is growing, not only in developing countries but also in the developed ones.

One of the consequences of concurrent use of herbal medicines and allopathic drugs is the possibility of interactions. HDI is one of the most important clinical

concerns in the concurrent consumption of herbs and prescription drugs. The necessity of poly-pharmacy in the management of most diseases further increases the risk of HDI in patients. The ability of intestinal and hepatic CYP to metabolize numerous structurally unrelated compounds, apart from being responsible for the poor oral bioavailability of numerous drugs is responsible for the large number of documented drug–drug and drug–herb interactions [2]. This is more so, considering that oral drug delivery is the most employed in the management of most disease conditions in which case, drug interaction alters both bioavailability and pharmacokinetic disposition of the drug. This alteration and the resulting poor control of plasma drug concentrations would particularly be of concern for drugs that have a narrow therapeutic window or a precipitous dose–effect profile [3]. The interaction of drugs with herbal medicines is a significant safety concern, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin), drugs with long-term regimens and which are used in the management of life-threatening conditions. The risk of adverse effects due to interactions between herbal products and conventional drugs is often underestimated by consumers due to lack of information on the safety of herbal preparations [2].

HDI was often unsuspected by physicians for several reasons. Most trained physicians lack adequate knowledge on herbal drugs and their potentials for drug interactions [4]; herbal products also vary considerably in compositions depending on the source and package [5]; most patients do not consider it necessary to disclose their herbal consumptions to physicians who themselves hardly inquire such [6]. Further challenges with herbal medications include scientific mis-identification, product contamination and adulteration, mislabelling, active ingredient instability, variability in collection procedures, and failure of disclosure on the part of patients [7]. It has become very difficult to identify the possibility of occurrence of an interaction due to:

- Availability and easy accessibility of large number of herbal products in the market,
- Presence of multiple components of various pharmacological properties in the herbs,
- Lack of data on the pharmacological action and mechanisms of interactions of herbal products [2],
- Misinformation on the actual label content of herbal products [6,7]
- Low potential of herb induced adverse effects

Aim, Search and Selection Criteria

The current review was aimed at providing an overview of known and recently reported HDI with interest in the evidence available and the mechanism thereof. The review was systematically conducted by searching the databases of MEDLINE, PUBMED and EMBASE libraries for original researches, and case reports on HDI using the following search terms or combinations thereof: “drug–herb,” “herb–drug,” “interaction,” “cytochrome P450,” “plant,” “extract,” “medicinal,” “concurrent administration,” “herbal and orthodox medicines.” Relevant search terms were employed to accommodate the various individual medicinal herbs employed in Africa, America, Asia, Europe, and Australia. The reported interactions and their mechanisms with orthodox medications were searched and collated. Searches were not limited by date or place of publications but to publications available in English language.

Drug interactions

Drug interaction exists when the usual effects of a drug is enhanced or diminished due to the presence of another foreign body/ xenobiotics in humans or animals. The impact of interaction may be positive that is, yielding an improved pharmacological effect, reduced toxicity, cost reduction, increased convenience; or negative, resulting in increased toxicity and reduced efficacy [8]. Interaction of drugs can be with other drugs [drug-drug interaction (DDI)], such as that seen with the interaction of antacids and protein pump inhibitors [9]. Interactions can also occur with herbs [drug- herbs interaction (DHI)] such as St John’s wort on drugs metabolized by CYP3A4 [10] or with food [drug – food interactions (DFI)] such as the effect of grapefruit on drugs [11], or due to disease conditions (drug -disease interactions) such as Cirrhosis on hepatic metabolism of drugs [12].

Herb Use and its Prevalence

The first World Health Organization Traditional Medicine Strategy assessed that approximately 80% of the population in Africa use some form of traditional medicine to cater for their health care needs while defining traditional medicine. It is the total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. This includes herbal medicines composed of finished herbal products, herbal preparations and the herbal materials that contain as active ingredients parts of plants, or other plant materials, or combination of all the parts. They can be used as complementary medicines alongside conventional orthodox medicine or as alternative medicine in place of conventional medicine and commonly referred to as complementary or alternate medicine (CAM). This could be attributed to limited access to conventional health care, easy access to the herbs as well as the common belief that herbs are all-natural and regarded as totally safe [13].

The use of herbs can be classified into its use as an herbal supplement and for the treatment of major and minor conditions. Results from the 2007 National Health Interview Survey showed that 3.9% of children and adolescent and 17.4% of adults used herbs and/or dietary supplements in the past survey [14]. According to a study among patients receiving treatment for chronic medical conditions in health centers in Cambodia and used herbal medicine for 12 months, 24.3% used herbs for acute problems, 56.9% used herbs for chronic problems and 18.6% used herbs to improve their overall health [15]. In a review of 20 studies carried out between 1995 and 2008 that involve the use of dietary supplements, 17-20% of people use herbal medicines as dietary supplements [16]. Study among cancer patients in a tertiary hospital in Sokoto, Nigeria shows that 28.3% of them use herbal therapy [17], 62% of type II diabetes patients questioned in a teaching hospital in Ethiopia were herbal medicine users [18]. A study among HIV/AIDS patients conducted in South Africa showed that 39% of the patients studied use herbal medicines for symptom management [19]. The use of herb is not limited to Africa, even in the "capital of the world"- USA, a study conducted among adults showed that 37% of the respondents in the study were currently using herb at the time of the study [20].

The use of herbs does not exclude vulnerable patients such as pregnant women. Pregnant women are known to go for the option of herbs when conventional medicine fails or as complements to conventional medicine. They use herbs also due to beliefs such as herbs are more effective than conventional medicine or that it is not harmful in pregnancy, or just because it is in their culture to use herbs. The greater accessibility and economic advantage compared to conventional medicine also aided its use [4]. 36.8% of pregnant women in Imo state-south eastern Nigeria, use herbs-Vernonia amygdalina and iron weed being the common herb of use [21]. In Mwanza, Tanzania, a quarter of women use herbs to induce labour during childbirth [22], studies have shown that in Ethiopia 73.1% of pregnant women receiving antenatal care at public health facilities in Hosanna town, as well as 48.6% at Gondar referral and teaching hospital used herbs [23,24].

There is little to no doubt that the use of herbal medicines is growing exponentially due to the common belief that herbs are "safe". From all these studies, it will be very convenient to state that use of herbs is continually on the rise and cannot be overlooked. With the growing interest in the use of the herb, the possibility of drug-herb interaction is inevitable.

Herb-Drugs Interaction (HDI)

Understanding HDI is of importance due to the high prevalence of herb use. This, as well as the presence of numerous pharmacologically active chemical entities, both known and unknown, in even a single herbal product have increased the probability of HDI occurring as compared to DDI. A lot of HDI have been identified to affect the pharmacological effects of drugs. However, researchers are beginning to go further to focus on identifying the exact mechanisms through which these herbs affect the pharmacological effect.

Enzyme-Mediated HDI: This is the most common causes of clinically relevant HDIs with a lot of studies to back it up. Methanolic extract of *Piper nigrum*, ethyl acetate extracts of Curcuma heyneana, Piper cubeba, *Piper nigrum* fruit and leaf, and *Zingiber aromaticum* inhibited the activity of the metabolism mediated by CYP3A with *Piper nigrum* showing the highest 91.7% inhibitory activity. Methanolic extract of *Catharanthus roseus, Punica granatum*, *Piper nigrum* fruit and leaf showed significant inhibitory activity against CYP2D6 with activity ranging from 69.1 to 98.1% [25]. Garden cress, Black seed inhibits CYP2D6 and CYP3A4 mediated metabolism in human liver microsomes and healthy human volunteers significantly [26,27]. Even honey, commonly regarded as the safest of all natural products, has been established to induce CYP3A4 enzyme activity [28]. Long time use of St John's wort and Ferula asafetida has been found to significantly induce CYP 3A4 metabolic activity [29].

Transporters-Mediated HDI: Studies have identified a number of clinically important transporter inhibitors including phytochemicals- reserpine, flavonoids, yohimbine, vincristine, vinblastine, alkaloids, furanocoumarins, quinidine, [30,31]. Some flavonoids like apigenin, kaempferol and quercetin inhibit the transporter functions of transporters localized in the apical membrane of the intestinal lumen. Flavonoids and stilbenes are classified as the third generation P-gp blockers and produce effects that are synonymous to those of the already known P-gp inhibitors like verapamil and cyclosporine [31]. Furthermore, green tea catechins, citrus and grapefruit juice affect the OATP-mediated transport of many ligands due to resveratrol found in low concentrations in grapes, berries nuts and red wine has been found to inhibit ABC transporter proteins. Modulation of P-gp by herbs such as *Hypericum perforatum* (St. John's wort), *Tapinanthus sessilifolius* (African mistletoe), *Coptis chinensis* (Chinese goldthread), *Vernonia amygdalina* (Bitter leaf), Ginkgo biloba (Maidenhair tree), *Piper nigrum* (Black pepper) and *Glycyrrhiza glabra* (Licorice) [32]. *Silybum marianum* (Milk thistle) competitively inhibits OATP1B3 and OATP2B1 due to the silybin [33].

Specific Examples of Herbs-Drug Interactions:

- **Drug Interactions with Ginkgo Biloba:** Ginkgo biloba is a popular herbal supplement promoted for sharpening memory and improving circulation. Ginkgo biloba is an

inhibitor of platelet activating factors thus making this supplement dangerous when taken with warfarin or other anticoagulant drugs. However, ginkgo biloba can also induce liver enzymes thus causing treatment failure with drugs that are metabolized by the cytochrome P-450 liver enzymes. A 55-year-old man suffered a fatal seizure leading to his death with no evidence of non-compliance of his drugs, phenytoin and valproic acid as evidenced by therapeutic range of both drugs for last one year. Autopsy report showed sub-therapeutic serum levels of phenytoin (2.5 mg/mL) and valproic acid (26 mg/mL), which was traced to his self-medication with ginkgo biloba. Ginkgo induces CYP2C9 and CYP2C19 activity that metabolizes phenytoin and valproic acid thus causing treatment failure [34].

- **Drug Interactions with Ginger and Garlic:** Ginger and garlic supplements are popular, but each supplement increases bleeding risk in patients taking warfarin. Ginger increases antiplatelet activity of nifedipine, a calcium channel blocker [35]. Garlic is widely used around the world for its pungent flavour as a seasoning or condiment. There is some scientific evidence that garlic can lower high cholesterol after a few months of treatment. Garlic seems to also lower blood pressure in people with high blood pressure and possibly slow "hardening of the arteries." There is also some evidence that eating garlic might reduce the chance of developing some cancers such as cancer of the colon and possibly stomach cancer and prostate cancer. Co-administration of garlic did not significantly alter warfarin pharmacokinetics or pharmacodynamics. However, subjects with the VKORC1 wild-type genotype showed an increase in the S-warfarin EC50 when warfarin was administered with garlic [36]. Interactions of Warfarin with Herbal supplements Warfarin therapy must be critically monitored by measuring INR because warfarin is known to interact with many drugs and herbal supplements. Warfarin acts by antagonizing the cofactor function of vitamin K. Although clinical efficacy of warfarin varies with intake of vitamin K and genetic polymorphisms that modulate expression of CYP2C9, the isoform responsible for clearance of S-warfarin, several herbal supplements also have significant effects on metabolism of warfarin. Herbal supplements that may potentiate the effect of warfarin thus increase the risk of bleeding include angelica root, arnica flower, anise, borage seed oil, bromelain, chamomile, fenugreek, feverfew, garlic, ginger, horse chestnut, liquorice root, lovage root, meadowsweet, passionflower herb, poplar and willow bark. Anticoagulant effect of warfarin also increases if combined with antiplatelet herbs such as danshen, and ginkgo biloba. Conversely, vitamin K containing supplement such as green tea extract may antagonize the anticoagulant effect of warfarin [37,38].
- **Drug Interaction with Baicalin:** Baicalin is a flavone glucuronide purified from the medical plant Radix scutellariae through uridine diphosphate glucuronidation. Nowadays, baicalin has begun to be used in bilirubin lowering therapy, both prescribed and over the counter, in China. The mean changes in AUC ratio of bupropion was lower for subjects with CYP2B6*6/*6 genotype compared with those with CYP2B6*1/*1 genotype following baicalin use, indicating baicalin-caused induction of CYP2B6-catalyzed bupropion hydroxylation. And administration of baicalin decreased the AUC of rosuvastatin by about 42%, 24%, and 1.8% in SLCO1B1 *1b*1b, *1b*15, and *15*15 carriers, respectively [39].
- **Drug Interactions with Grapefruit Juice:** Grapefruit juice and grapefruit in general, is a potent inhibitor of the cytochrome P450 CYP3A4 enzyme, which can affect the metabolism of a variety of drugs, increasing their bioavailability. In some cases, this can lead to a fatal interaction with drugs like astemizole or terfenadine. Grapefruit juice treatment significantly increased total AUC of lansoprazole in CYP2C19 PMs (*2, *3), and the total AUC of lansoprazole sulfonic/lansoprazole was significantly decreased in CYP2C19 homozygous EMs (*1/*1) [40]. Homozygous wild types of ABCB1 3435C>T but not the other genotypes showed a significant decrease in the active metabolite carebastine urinary excretion after grapefruit juice [40].

Conclusion

Concurrent 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. Modern technology has been used to clarify benefits and risks of herb-drug interaction achieved upon concurrent administration. Prescribers should obtain full medication history of patients and must be fully concerned about their therapeutic regimens. Currently, herb-drug interactions are of major global health importance, particularly in Africa, where herbal medicine is widely practiced, and there is very limited information on the extent of herb-drug interactions. More herb- drug interaction research in Africa is advocated so that a significant data base can be developed just as seen with conventional medicines. This will help to improve our understanding of herb-drug interactions and their pharmacokinetic mechanisms will enable us to predict better, evaluate, and manage potential

risks associated with concurrent use of herb and drug-based therapies.

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