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Clinical Herb-Drug Interactions as a Safety Concern in Pharmacotherapy

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Herbal medicines are plant-derived substances or extracts and are classified as herbs, finished herbal products, herbal materials and preparation[1,2]. There are over 35,000 plants that are used as herbal medicines. Thousands of herbal products can be bought over the counter. It is estimated that one third of American use herbal supplements to treat illness or improve health. In a survey of 61,587 participants, between the ages of 50 to 77 years, identified that approximately 30% of men and women use medicinal herbs in the state of Washington[3]. In another study of 5,456 of herbal users, they reported that only one out of three adults disclose their herbal uses to their healthcare provider[4]. Also, individuals with more than 2 chronic conditions or 4 clinic visits are more likely to use herbal supplements. Presently, herbs are marketed as dietary supplements and are not regulated similar to conventional drugs[5]. Due to the Dietary Supplement Health and Education Act (DSHEA) of 1994, the Food and Drug Administration (FDA) of US does not require the sponsors to conduct well randomized and controlled clinical trials to obtain the safety and efficacy data for dietary supplements before marketing, although a pre-market review of the safety data is always warranted. If the dietary supplement contains a new ingredient, that ingredient will be reviewed by FDA (not approved) prior to marketing — but only for safety, not effectiveness. There are very limited safety and efficacy data or no such data for most marketed herbal medicines. According to the DSHEA, manufacturers, packers, and distributors of dietary supplements in the United States are required to report information about serious adverse effects associated with the use of these supplements to the FDA.

The biggest concern of herbal medicines is adverse effects. In 2008, the FDA had identified 948 reports of adverse effects from dietary supplements[5]. Approximately 6,300 people nationwide complained about adverse reactions to dietary supplements between 2008 and 2012 (about 1,000 events per year), according to FDA statistics (http://www.fda.gov/Food/DietarySupplements/ReportAdverseEvent/). More than 9,700 recalls of dietary supplements were requested by the FDA between 2008 and 2012. Due to underreporting, it is estimated that there are potentially 8,000 – 16,000 adverse effects associated with dietary supplementary consumption per year in the US[6]. Herbal medicines have the potential to interact with prescription drugs, resulting in adverse effects by changing the pharmacokinetic and pharmacodynamics profiles of prescription drugs[7-14]. Understanding the interaction of herbs and conventional drugs will help better inform the public to prevent adverse effects.

Herbal medicines may either induce or inhibit the cytochrome P450s (CYPs) and P-glycoprotein (P-gp), which may change the clearance and excretion of drugs[15-17]. CYPs are a diverse set of enzymes that metabolize xenobiotic substances, such as drugs, chemicals, and toxins. CYPs play a major role in deactivating these substances by oxidization, which is necessary for xenobiotic clearance. Although CYPs are able to oxidize many substances, they can either be deactivated or induced by exogenous substances. (P-gp), a multidrug resistance protein, can secret a number of drugs back into the intestinal lumen limiting their oral absorption and canrestrict the distribution of drugs into the brain[18]. Herbal medicine can either induce or deactivate these proteins, resulting in unfavourable effects, along with disrupting the therapeutic doses of prescribed drugs[15-17, 19, 20].

Herbal medicines are not regulated as prescribed drugs by the FDA and can be readily obtained from the counter or online[8]; and patients may take herbal medicines in conjugation with prescribed drugs when they consider the combined usesafe or at least unharmful. Prescribed drugs with narrow therapeutic indices may lose their beneficial effects when the activities of CYPs or P-gp are altered by coadministered herbal medicines. Drugs with narrow therapeutic indices are amitriptyline, cyclosporine, digoxin, midazolam, and warfarin. The most common herbs that are found to be reactive to drugs with narrow indices are garlic, ginger,

ginkgo, ginseng, and St. John's wort[8-13]. These herbal medicines can altered the therapeutic dose of prescribed drugs. For example, garlic is used to treat hypercholesterolemia. The organosulfur compounds in garlic have many pharmacological properties, such as antibacterial, antiviral, and antihypertensive activities[21]. Although garlic possesses these beneficial properties, garlic extracts are found to have inhibitory effects on P-gp[22]. A study showed that garlic supplements affect the bioavailability of saquinavir, a HIV protease inhibitor, reducing its AUC by 41% and the mean maximum concentration by 54% in ten healthy volunteer[23]. Saquinavir is a substrate for P-gp, which suggests that garlic impact on the bioavailability may be due to its influence on P-gp[24,25]. Another common herb is the Chinese traditional medicine Kangen-Karyu (KGK , Guan-Yuan-Ke-Li in Chinese and has been developed in Japan via the modification of herbal constituents of Kan-shin no. 2), which is used to dispel blood stasis as a treatment for cardiovascular diseases such as angina pectoris and cerebrovascular disorders[26]. KGK contains 6 herbs peony roots, cnidium roots, safflower roots, Saussure roots, and Danshen[27]. KGK was found to suppress the metabolism and elimination of warfarin, leading to a prolonged bleeding[28]. One possible cause of this side effect is the ingredient Danshen, which was showed to have inhibitory effects on CYP1A2, 2C9, and 2D6[29]. Gingko also has similar inhibitory effects on theses cytochrome enzymes and prolong swarfarin-induced bleeding in patients[30,31]. Ginkgo is used to treat memory impairment. It is found that it reduce the symptoms of dementia and also have the potential to treat cardiovascular diseases[32,33]. Despite the potential medical uses, ginkgo interacts with a number of drugs such as thiazide diuretics and trazodone[34]. Ginkgo is found to increase blood pressure when combined with thiazide diuretics. Ginseng is an herbal supplements that is widely used in many products, such as energy drinks. It is found to induces mania when combined withthe non-selective and irreversible monoamine oxidase inhibitor, phenelzine[10]. These examples display the various multiple herb-drug interactions, which can have moderate to serious biological and clinical effects. It is important to identify the herbs that are interacting with the drug to prevent dangerous clinical outcomes. Further studies are needed to address the mechanisms and clinical significance of these herb-drug interactions.

Herbal medicines often contain over 150 ingredients, which present a problem in identifying the cause of adverse effects. Herbal medicines can contain contaminants, which includes chemicals, heavy metals, toxin, and pesticides[35]. These ingredients can mimic or disrupt the effects of the prescribed drugs on its targets[36,10]. Identifying the active ingredients may be time-consuming and labor intensive. There are many types of drugs that interact with herbal supplements. This includes anticoagulants, antidepressants, anti-HIV agents, anticancer drugs, cardiovascular drugs, immunosuppressants, and sedatives[14]. These drugs are often administered orally and are often used to treat chronic illness[37]. Small changes in the plasma concentration and AUC of the drug may alter its therapeutic effects in patients who taking both herbal medicine and the drug[8,14].

Herbal medicines will continue to be used worldwide. There is a misconception that herbal supplement are natural products, deeming them safe to use[38]. Presently, there is limited information on the characterization of the in vivo disposition and pharmacologic actions of most herbal medicine, making the clinical herb-drug interactions difficult to anticipate and predict. Additionally, because of the thousands of available herbal products in the market, herbal-drugs interaction occurs very frequently. Therefore, it is important that clinicians inform patients of possible interaction of herbal supplement with their-medication regimens[39].

One potential strategy is to identify the unique chemical properties and structural requirements of main herbal components that have a high potential to interact with CYPs, P-gp, or other proteins that are involved in drug metabolism and excretion[39]. The structures that have a potential to cause herb-drug interactions should possess at least one of the following properties: 1) a cytochrome P450 substrate, 2) a P-gp substrate, and 3) an inducer or inhibitor of CYP enzymes. Along with identifying the herbal medicine properties, clinicians should monitor patient's drug regimen and adjust dosage of prescribed drugs when necessary if patients are taking herbal supplements. Clinicians should urge patients to avoid herb supplements if they are taking drugs with a narrow therapeutic window.

The combination of herb and prescribed drugs remains a safety issue because of the potential of toxic or lethal adverse eventsdue to changes in the pharmacokinetics and/orpharmacodynamicsof the prescribed drug. Therefore, clinicians should obtain or have access to the medication history of the patients that includes both prescription and over-the-counter medications. Also, clinicians should understand the risk of potential drug-herb interactions, so they can develop strategies to minimize potential adverse events in a timely manner. Furthermore, it is important for patients to disclose their herb supplement uses and remain attentive to their prescribed drug regimens.

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