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REVIEW

Herb-drug enzyme-mediated interactions and the associated experimental methods: a review

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Abstract

OBJECTIVE: To review the interactions between herbs and widely used drugs and summarize the associated experimental methods.

METHODS: Definite herb-drug interactions were obtained by searching PubMed, other large overseas databases and summarizing new researches from China. We summarize some methods to assess the interaction between herbs and drugs involving microsomal, cell culture and animal experiments, and clinical trials, classifying this method as single ingredient herbs, crude herb extracts, and herbal formulae.

RESULTS: Many herbs interact with drugs through a complex cytochrome P450 and/or P-glycoprotein mechanism. Herb-induced enzyme inhibition and/or induction may result in enhanced and / or decreased plasma, tissue, urine and bile drug concentrations, leading to a change in a drug's pharmacokinetic parameters and resulting in the improper treatment of patients and potentially severe side effects. Use of an appropriate method for comprehensively assessing herb-drug interactions can minimize clinical risks. Different methods were used by researchers to assess the pharmacological changes of drugs *in vivo* and *in vitro* and the mechanisms of the interactions from microsomal, cell culture and animal experiments, and clinical trials are discussed in this review.

CONCLUSION: Co-medication with herbs can result in changes in pharmacological effects of many drugs. This review describes the assessment of single-ingredient herbs, crude herb extracts, and herbal formulae. When choosing a research method to investigate herb-drug interactions, the properties of the drugs and herbs should be considered.

Key words: Herb-drug interaction; Metabolism; Cytochrome P-450 enzyme system; P-glycoprotein; Review

INTRODUCTION

Herbal medicines have been used for more than 5000 years.[1] However, in ancient times only single herbs

were ingested.[2] Today, herbal medicines are frequently used, especially among women and patients with chronic diseases.[3] Approximately 15%-20% of individuals taking prescription medications use herbal supplements. However, fearing censure, they may not be forthcoming to their physicians about their personal use of herbal medicines, even if they experience severe side effects.[4-6]

The interactions between herbs or dietary supplements and drugs requires attention, especially for the elderly, frail, or those taking multiple medications for chronic diseases.[7] Several important foods such as grapefruit juice, and herbals such as Yinxingye (*Ginkgo biloba. L*) have been reported to cause clinically significant adverse drug reactions.[8] Ginkgo products administered concurrently with aspirin, warfarin (Coumadin), or ticlopidine (Ticlid) interact and can cause bleeding. Additionally, St. John's wort (SJW)[9] and antidepressants administered together cause side effects such as gastrointestinal disturbances and allergic reactions.

The safety of herbs is mostly dependent on empirical experience, but these observations are not always effective at limiting side effects. Sometimes, the first signs of adverse effects take a long time to be recognized or they are recognized even after the patient has stopped using the herbs. Additionally, the ingestion of herbs is easily overlooked, therefore more publicly available information should be provided.[10] Extensive research into herb-drug interactions should be conducted to provide more information for patients and health care providers.

A search of PubMed into the study of herb-drug interactions revealed that the choice of methods can have a profound impact on the experimental results, primarily because of the complex mechanisms involved. Herein, we summarize the methods used to study the interactions of individual herbal ingredients, crude herb extracts, and herbal formulas with drugs, and their mechanisms of action, and classify the experiments according to the different models employed.

Mechanisms of herb-drug interactions

Drugs usually contain single chemical entities, while almost all herbal products contain mixtures of pharmacologically active constituents. As such, herb-drug interactions could occur more frequently than drug-drug interactions,[11] and the mechanism of herb-drug interactions may be more complex. *In vitro* and *in vivo* studies, clinical trials and case reports demonstrated that herbal agents, particularly SJW and Yinxingye (*Ginkgo biloba.* L), interact with several prescribed medications and affected their pharmacokinetic profiles. In most herb-drug interactions, the cytochrome P450 (CYP450) system and the efflux drug transporter P-glycoprotein (P-gp) play an important role.[1] More than half of the herbs ingested likely interact with the CYP system, which is also responsible for metabolizing many medications that inhibit and induce drug metabolism, and the P-gp, which is also important in herb disposition.

Research suggests that the mechanisms regulating herb-drug interactions often involve CYP isoforms. For example, studies on SJW used various animal models to study the different mechanisms involving CYP3A4, CYP2C19, and P-gp. The results indicated that the interactions observed *in vivo* with different drugs was similar to those observed using animal models.[12-17] The relative abundance of the CYP isoforms are 30% CYP3A4, 13% CYP1A2, 7% CYP2E1, 4% CYP2A6, 2% CYP2D6, 20% CYP2C, and 1% CYP2B6 in human hepatic smooth endoplasmic reticulum where 50% of drug metabolism occurs via CYP3A4, followed by 25% CYP2D6 and 20% CYP2C.[18] In these studies, CYP3A4 mainly mediated the drug interaction via the CYP system, especially for SJW.

The mechanisms of herb-drug interactions also involve different transport proteins, especially P-gp. P-gp, an ATP (adenosine triphosphate)-dependent membrane transporter,[19] is expressed in a broad range of tissues including the colon and intestinal mucosa, blood-testis capillary epithelial cells, liver cells, the adrenal gland and kidney proximal tubules. It works to decrease the oral absorption, intracellular concentration and bioavailability of xenobiotics.[20,21] In the ATP binding cassette (ABC) family, P-gp is the largest subgroup, which also includes multidrug resistance-associated protein P1 (MRP1) and ABCG2.[22] Most of the interactions between herbs and drugs is P-gp-mediated, while interactions with other drugs, such as baicalein, involves MRP1, MRP2 and ABCG2.[23]

In vitro research studies were conducted to assess the activity of the enzymes involved by determining the cytoplasm or the microsome involvement, and these were sometimes followed by *in vivo* studies that assessed the herb-drug interactions. Not all studies investigate the herb-drug interactions at the metabolism level, but still provide useful information. For example, Aurantium caused enhancement of gastrointestinal motility at the peak plasma concentrations of amiodarone.[24] Additional studies may be required to determine the mechanisms involved.

Summary of the experimental methods used to study the interactions of single component herbs with drugs

Studying single herb components can provide specific information about the nature of the herb and its mechanism of interaction. Research on Chuanxinlian (*Herba Andrographitis Paniculatae*) extract and its major component, andrographolide, which interacts with theophylline, showed that certain components other than andrographolide inhibited theophylline elimination in rats, and that the mechanism involved andrographolide-induced induction of CYP1A2.[25] Thus, studies of the isolated herb component provided useful information on its mechanism of action. A total of 28 single herb components known to interact with drugs are listed in Table 1. The information has come from clinical