Review

Pharmacodynamic and pharmacokinetic interactions between herbs and western drugs

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SUMMARY

In recent years, the combined use of Herbal medicines and Western drugs has been increasing. Though certain problems may occur when both types of medicines are taken together, they have not been adequately analyzed. It was reported that anticoagulation was enhanced in addition to bleeding when patients took long-term warfarin therapy in combination with Salvia miltiorrhiza (danshen), and laxative herbs accelerate intestinal transit and interfere with the absorption. Herbal constituents, curcumin, ginsenosides, piperine, catechins and silymarin were found to be inhibitors of P-glycoprotein. St John’s wort induces the intestinal expression of P-glycoprotein. Anthraquinone, quercetin and coumarins were found to be a potent inhibitor of P-450. Glycyrrhizin or liquorice extracts, Garlic and St John’s wort are a potent inducer of CYP3A4. This review provides a critical overview of interactions between herbal medicines and other drugs. Hence, it is necessary to study the pharmacodynamic and pharmacokinetic interactions of many herbal medicines between western drugs

Key words: Herbal medicine; Drug interaction; Pharmacokinetic; Pharmacodynamic; P-glycoprotein; P-450; CYP3A4

INTRODUCTION

Herbs and preparations have been used to treat ailments since medicine began. The treatment of diseases with medicines of plant origin is an integral part of many cultures throughout the world. The most ancient plants thought to be of medical significance were discovered in prehistoric graves and are 60,000 years old. In recent years, the combined use of Herbal medicines and Western drugs has been increasing. Though certain problems may occur when both types of medicines are taken together, they have not been adequately analyzed. It is reported that some of herbal medicines such as St. John’s wort, garlic, ginseng, and gingko, have given rise to clinical interactions when co-administered with prescription medicines. Such adversities have spurred various pre-clinical and in vitro investigations on a series of other herbal remedies. In this review, pharmacokinetic and pharmacodynamic studies that have been conducted for some of more important or widely used phytopharmaceuticals are critically evaluated. Furthermore, various drug interactions are discussed, showing that caution should be
exercised when combining phytopharmaceuticals with chemically derived active pharmaceutical ingredients.

**Drug interactions between herbal and prescription medicines**

Interactions between herbal and prescription medications may be caused by either pharmacodynamic or pharmacokinetic mechanism. Pharmacodynamic interactions may occur when constituents of herbal products have either synergistic or antagonist activity in relation to conventional drugs. As a result, concentration-dependent activity of a therapeutic molecule is altered on the site of action at the drug-receptor level. Pharmacokinetic interactions result from alteration of absorption, distribution, metabolism, or elimination of a conventional drug by a herbal product or other dietary supplements. To date, several pharmacokinetic drug-herb interactions (absorption, distribution, and metabolism) and additive pharmacodynamic interactions have been identified.

**Pharmacodynamic interactions**

Pharmacodynamic interactions can occur when a herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma concentration of either herbal product or drug. Pharmacodynamic interactions are related to the pharmacologic activity of interacting agents and can affect organ systems, receptor sites, or enzymes. A pharmacodynamic interaction may occur when herbs that possess antiplatelet activity are administered with anticoagulant drugs, thus increasing the risk of bleeding. The antiagulant action of warfarin is enhanced by ginkgo (*Ginkgo biloba*) and possibly by many other herbs, such as Danshen (*Salvia miltiorrhiza*), Dong quai (*Angelica sinensis*), Galic (*Allium sativum*) and *Panax Ginseng* (Fugh-berman and Ernst, 2001). Regarding effects of angelica root with warfarin, angelica root affects not the pharmacokinetics but the pharmacodynamics in rabbits (Lo *et al.*, 1995; Page and Lawrence, 1999). Other examples of animal studies with barbiturates, pentobarbital and hexobarbital, and other non-barbiturate CNS-depressants like urethane and glutethimide suggest not simply additive but synergistic effects with kavalactones (Klohs *et al.*, 1959; Meyer, 1962; Jennifer and Ramzana, 2004), and *G. biloba* may act as an antagonist on gamma-aminobutyric acid (GABA) activity at benzodiazepine binding sites (Huang *et al.*, 2004; Mary *et al.*, 2006).

**Pharmacokinetic interactions**

Pharmacokinetic herb-drug interactions are due to altered absorption, metabolism, distribution and excretion of drugs. The primary mechanism of absorption is passive diffusion of nonionized drug molecules via the lipophilic gastrointestinal (GI) mucosa. Therefore, drugs that change pH, gastric emptying time, or GI motility will interact with the absorption of other agents. The most popular stimulant laxative herbs of the anthranoid-containing senna (*Cassia senna* and *C. angustifolia*), cascara sagrada (*Rhamnus purshiana*), aloe vera (*Aloe barbadensis*), frangula (*Rhamnus frangula*), yellow dock (*Rumex crispus*), and Chinese rhubarb (*Rheum officinale*) will accelerate intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drugs (Westendorf; Adriane, 2000). It is well-known that metal ions and tannic acid present in herbal medicine form insoluble chelates or complexes with some western drugs such as antibiotics, isoniazid and levodopa, resulting in reduction of drug absorption (Chan and Cheung, 2000). It is also reported that alkaloids or other flavonoids form precipitates with some western drugs containing aluminium, bismuth, calcium, ferrous and magnesium ions. More recently, induction and inhibition of intestinal P-glycoprotein have been described in significant drug interactions. The P-glycoprotein drug transporter is a glycoprotein encoded by the MDR1 gene and functions as a transmembrane efflux transporter that pumps
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Drugs out of cells (Zhou et al., 2004). P-glycoproteins are found in many tissues and especially in organs responsible for drug absorption or elimination, such as the intestine, liver, and kidneys (Horn et al., 2002). P-glycoprotein is vulnerable to inhibition, activation, or induction by herbs and herbal constituents. Curcumin, ginsenosides, piperine, some catechins from green tea, and silymarin from milk thistle were found to be inhibitors of P-glycoprotein (Zhou et al., 2004). St John’s wort induces the intestinal expression of P-glycoprotein (Izzo, 2004). Drug metabolism is divided into 2 categories of phase I and phase II transformation reactions. Phase I reactions include oxidation, hydrolysis, and reduction, resulting in a compound that is generally less toxic and more hydrophilic, allowing for easy excretion. Phase II reactions primarily result in termination of biologic activity of the drug. Phase II transformation reactions include glucuronidation, sulfation, acetylation, and methylation (Shannon et al., 2005). The CYP450 is the most important phase I drug-metabolizing enzyme system and it is a family of monooxygenase enzymes that are mainly found in intestinal and liver cells and catalyzes several Phase I metabolic processes including oxidation, hydroxylation, S- and O-demethylation, and oxidative deamination. Many herbs and natural compounds isolated from herbs (e.g., flavonoids, coumarins, furanocoumarins, anthraquinones, caffeine and terpenes) have been identified as substrates, inhibitors or inducers of various CYP enzymes (Ioannides, 2002) (Table 2).

Induction of CYP450 enzymes occurs when a drug stimulates the synthesis of more enzyme proteins, enhancing the enzyme’s metabolizing capacity. In studies conducted with mice, glycyrrhizin

Table 1. Pharmacodynamic interaction between herbal and prescription medicines

<table>
<thead>
<tr>
<th>Herb</th>
<th>Drug</th>
<th>Result of interaction</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginko</td>
<td>Aspirin</td>
<td>Spontaneous hyphema</td>
<td>Additive effect on platelet aggregation (Matthews, 1998)</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Over - anticoagulation</td>
<td>Additive effect on coagulation mechanism (Matthews, 1998)</td>
</tr>
<tr>
<td>Ginger</td>
<td>Phenprocoumon</td>
<td>Over - anticoagulation</td>
<td>Additive effect on coagulation (Kruth et al., 2004)</td>
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<tr>
<td>Danshen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ding quai</td>
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<td></td>
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<tr>
<td>Gallic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginseng</td>
<td>Warfarin</td>
<td>Over - anticoagulation</td>
<td>Additive effect on coagulation mechanism (Rosado, 2003; Jiang et al., 2004; Janetzky et al., 1997)</td>
</tr>
<tr>
<td>Curcicion</td>
<td></td>
<td></td>
<td>Curbicine containing vit E, which can antagonize vit K (Yue et al., 2001).</td>
</tr>
<tr>
<td>Green tea</td>
<td>Alprazolam</td>
<td>Semicomatose state</td>
<td>Additive effect on GABA receptors (Almeida et al., 1996).</td>
</tr>
<tr>
<td>Kava</td>
<td>Levodopa</td>
<td>Reduced efficacy of levodopa</td>
<td>Kava possessing dopaminergic antagonistic properties (Schelosky et al., 1995)</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>SRI (serotonin-reuptake inhibitor-sertraline, parozitine, nefazodone and venlafaxin)</td>
<td>Serotonergic syndrome</td>
<td>Synergistic effect on 5-HT uptake (Gordon et al., 1998; Lantz et al., 1999; Prost et al., 2000)</td>
</tr>
<tr>
<td></td>
<td>Buspirone</td>
<td>Hyponania</td>
<td>Synergistic effect on 5-HT receptors (Dannawi et al., 2002)</td>
</tr>
</tbody>
</table>

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or liquorice (Glycyrrhiza uralensis) extracts elevated the metabolism of diagnostic substrates associated with CYP3A, and increased the activity of CYP2B, CYP1A2 and CYP2A1 (Paolini et al., 1999). Garlic may induce hepatic CYP3A4 metabolism of saquinivir resulting in decreased plasma drug levels (Piscitelli et al., 2002). St John’s wort (Hypericum perforatum) is a potent inducer of CYP3A4 and involved in the most severe drug-herb interactions. The protease inhibitors, cyclosporine, warfarin, digoxin, oral contraceptives, and many other medications can be rendered ineffective with concomitant use of St John’s wort (Zhou et al., 2004). Inhibition of CYP450 enzymes may occur secondary to competitive binding between two drugs or to permanent inactivation (Shannon, 2005). Generally, inhibition begins after the first dose of the inhibitor and the length of inhibition correlates with the half-life of the drug.

Discontinuation of the inhibitor will usually cause a decreased serum concentration of other drugs metabolized by that enzyme, whereas discontinuation of an inducer will result in an increased serum concentration and risk of toxicity. In vitro investigations, commercial ethanolic extracts of many herbs extensively inhibit the CYP3A4-mediated debenzylation of benzyloxyresorufin (Budzinski et al., 2000). Similarly, hot water decoctions or 40% ethanol infusions of many herbal remedies impair CYP3A activity (Guo et al., 2001). The phytochemical anthraflavic acid, a planar anthraquinone, is a potent inhibitor of hepatic CYP1A activity in vitro (Ayrton et al., 1987). Quercetin was found to be a potent inhibitor of CYP-450 (Breinholt et al., 1999; Sousa and Marletta, 1985). Inhibitory effects of quercetin on CYP1A2 and CYP2C8 have been reported (Dierks et al., 2001). Coumarins, which are

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</tr>
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<tbody>
<tr>
<td>St John’s wort</td>
<td>Digoxin</td>
<td>Decreased plasma digoxin concentration</td>
<td>St John’s wort induces p-glycoprotein involved in digoxin absorption and excretion.</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>Decreased plasma simvastatin concentration</td>
<td>Simvastatin is a substrate of p-glycoprotein and metabolized by CYP enzymes. Both CYP enzymes and p-glycoprotein are induced by St John’s wort.</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Decreased anticoagulant effect</td>
<td>Warfarin is metabolized by CYP enzymes which are induced by St John’s wort.</td>
</tr>
<tr>
<td></td>
<td>Phenprocoumon</td>
<td>Decreased anticoagulant effect</td>
<td>Phenprocoumon is metabolized by CYP enzymes which are induced by St John’s wort.</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Decreased bioavailability of verapamil</td>
<td>Induction of intestinal CYP3A4 by St John’s wort.</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>Decreased plasma levels of alprazolam</td>
<td>Alprazolam is specific probe for CYP3A4 induced by St John’s wort.</td>
</tr>
<tr>
<td>Kaba</td>
<td>Alprazolam</td>
<td>Semicomatose state</td>
<td>Kaba inhibits CYP3A</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Warfarin</td>
<td>Over-anticoagulation</td>
<td>Cranberry flavonoids CYP enzyme</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Midazolam</td>
<td>Decreased systemic midazolam clearance</td>
<td>Echinacea inhibits intestinal CYP3A4.</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>Decreased caffeine oral clearance</td>
<td>Caffeine is a substrate of CYP which is inhibited by Echinacea</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Nifedipine</td>
<td>Decreased systemic nifedipine clearance</td>
<td>Furanocoumarines inhibit CYP enzyme.</td>
</tr>
<tr>
<td></td>
<td>Pimozide</td>
<td>Decreased systemic pimozide clearance</td>
<td>(Mohri et al., 2001)</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Decreased systemic felodipine clearance</td>
<td>(Yee et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>Decreased systemic alprazolam clearance</td>
<td>(Markowitz et al., 2003; Markowitz et al., 2004)</td>
</tr>
</tbody>
</table>

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contained in grapefruits, effectively and selectively inhibit and inactivate several cytochrome P450 enzymes (Cai et al., 1993). The furanocoumarins such as notopterol and paradisin were reported to inhibit a specific human drug metabolizing enzyme, cytochrome P450 3A (CYP3A) from activity (Mëenpää et al., 1993; Guo et al., 2000). Grapefruit juice has been found to significantly increase oral bioavailability of most dihydropyridines (e.g., felodipine), terfenadine, saquinavir, cyclosporine, midazolam, triazolam and verapamil (Yee et al., 1995; He et al., 1998; Bailey et al., 2000; Mohri and Uesawa, 2001; Ioannides, 2001). A new CYP3A4 inhibitor, paradisin C, was recently isolated from grapefruit juice (Ohta et al., 2002). These results, therefore, raised the concern that the furanocoumarin containing oriental medicines may alter pharmacokinetics of co-ingested drugs similar to the case with grapefruit juice. The hot-water extract of Angelica dahurica root (Angelica dahurica Benth. et Hook.) exhibited the potential to affect the metabolism of other drugs by liver cytochrome P450 (Ishihara et al., 2000).

Conclusions and future prospects
Cases have been published reporting enhanced anticoagulation and bleeding when patients took long-term warfarin therapy in combination with Salvia miltiorrhiza (danshen). Laxative herbs, anthraquinone contained in senna, cascara sagrada, aloe vera, frangula, yellow dock, and Chinese rhubarb (Rheum officinale) will accelerate intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drugs. It is well-known that metal ions and tannic acid present in herbal medicine form insoluble chelates or complexes with some western drugs such as antibiotics, isoniazid and levodopa, resulting in reduction of drug absorption. P-glycoprotein appears to limit the cellular transport from intestinal lumen into epithelial cells and also enhances the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space. Curcumin, ginsenosides, piperine, catechins, and silymarin were found to be inhibitors, but St John’s wort is an inducer of P-glycoprotein. The CYP450 is the most important phase I drug-metabolizing enzyme system. Glycyrrhizin or liquorice extracts, garlic and St John’s wort are potent inducers of CYP3A4. Ethanolic extracts of many herbs extensively inhibit the CYP3A4. Angelica dahurica root and herbal constituents of anthraquinone, quer cetin, coumarins, and furanocoumarin inhibit and inactivate a number of cytochrome P450 enzymes.

An extensive review of the literature identified the reported herb-drug interactions with clinical significance, many of which are from case reports and limited clinical observations. The interactions mentioned above make up merely a small percentage of possible drug interactions. A lot of work is still required to be done in systematic investigations for the interactions between herbal and modern drugs. Hence, it is necessary to study the pharmacodynamic and pharmacokinetic interactions of many herbal medicines between western drugs to identify the safety, the efficacy or risk of side effects in clinical use.

REFERENCES


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