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Pharmacokinetic herb–drug interactions with traditional Chinese medicine: progress, causes of conflicting results and suggestions for future research

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ABSTRACT

Traditional Chinese medicine (TCM) has a long history of medical use in China and is still used worldwide. Unexpected herb–drug interactions (HDIs) may lead to adverse drug reactions or loss of therapeutic efficacy of the victim drug. Here, based on searches of Medline, EBSCO, Science Direct and Web of Science using various keywords, we summarize the TCM-derived pharmacokinetic HDIs that were reported from 1990 to 2015 and discuss the underlying mechanisms. In general, many pre-clinical and clinical pharmacokinetic HDIs have been reported. Our searches show that TCMs cause pharmacokinetic interactions with therapeutic drugs mainly by inhibiting or inducing drug-metabolizing enzymes and transporters. However, most of the interactions result from a small number of prescription medications and the actual potential for harm is low. Moreover, such HDIs can be avoided by discontinuing the TCMs. Despite the extensive number of reports on TCM-derived HDIs, the findings are frequently conflicting and can be confusing. The causes of the conflicts vary, but we classified them into three basic categories as follows: (1) complicated nature and poor quality control of TCMs, (2) different responses of various test systems to TCM exposure and (3) diverse study designs. Accordingly, we propose rational study designs for future HDI research. We also propose that a specific authoritative guide be established that provides recommendations for HDI studies. This review provides insights into the progress and challenges in TCM-derived pharmacokinetic HDI research.

ARTICLE HISTORY

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KEYWORDS

CYPs; herb–drug interaction; p-glycoprotein; pharmacokinetic interaction; study design; traditional Chinese medicine

Introduction

Herbal medicines are believed to be "all natural" with fewer side-effects, better patient compliance, relatively low cost and high accessibility (Abad et al., 2010); hence, they are popularly applied in clinics, especially for chronic and severe diseases such as anxiety and depression (Meeks et al., 2007), diabetes mellitus (Halat & Dennehy, 2003), cardiovascular diseases (Tachjian et al., 2010), acquired immune deficiency syndrome (Langlois-Klassen et al., 2007) and cancers (Yang et al., 2010). It was estimated that about 15% of patients in the US ever take herbal medicines concomitantly with prescription medications (Bush et al., 2007). In other countries, the ratio varies from 19.3% to 49.5% (Djou et al., 2013; Giveon et al., 2004; Picking et al., 2011). However, like drug–drug interactions (DDIs) (McDonnell & Jacobs, 2002), unexpected herb–drug interactions (HDIs) may lead to adverse drug reactions (ADRs) (Bilgi et al., 2010; Chiang et al., 2005; Kupiec & Raj, 2005) or to the loss of therapeutic efficacy of the victim drug. In a national survey sponsored by the US Food and Drug Administration, there were approximately 73% of the adult US populations were the users of any supplement and 4% of them had experienced related adverse events (Timbo et al., 2006). In another survey, 7% of the co-users of herbal medicines and prescription medications had experienced adverse effects (Bush et al., 2007).

Recently, HDIs have been attracting increasing attention for the following reasons: (1) herbal medicines are frequently used worldwide (Gardiner et al., 2006); (2) prescribed and non-prescribed herbal medicines are commonly used together in hospitalized (Goldstein et al., 2007) and non-hospitalized patients (Qato et al., 2008), but patient–physician communication about the use of herbal medicines is insufficient (Shelley et al., 2009), and physicians’ knowledge of and personal experiences with herbal medicines limit their ability to assist their patients (Xu & Levine, 2008); (3) the likelihood of HDIs is theoretically higher than the likelihood of DDIs since herbal medicines contain more than one com-
Table 1. Mechanisms of TCM derived pharmacokinetic HDIs.

<table>
<thead>
<tr>
<th>ADME</th>
<th>Targets</th>
<th>Representative TCMs and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Intestinal CYPs</td>
<td>Schisandrae Chinensis Fructus [Schisandra chinensis (Turcz.) Baill.] (Lai et al., 2009); Silybi Fructus [Silybum marianum (L.) Gaertn.] (Brantley et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Intestinal UGTs</td>
<td>Ginkgo Folium (Ginkgo biloba L.) (Mohamed &amp; Frye, 2010); Glycyrrhiza Radix et Rhizoma (Glycyrrhiza uralensis Fisch.) (Moon &amp; Kim, 1997)</td>
</tr>
<tr>
<td></td>
<td>Intestinal P-gp</td>
<td>Rhe Radix et Rhizaoma (Rheum palmatum L.) (Yokojo et al., 2010); Schisandrae Chinensis Fructus [Schisandra chinensis (Turcz.) Baill.] (Jiang et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>Other intestinal transporters</td>
<td>Rubi Fructus (RRubus chingii Hua) and Ginkgo Folium (Ginkgo biloba L.) (Fuchikami et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>Intestinal pH value</td>
<td>Atractylodis Rhizoma [Atractylodes lancea (Thunb.)DC.] (Satoh et al., 2000)</td>
</tr>
<tr>
<td></td>
<td>Gastric emptying and intestinal transit time</td>
<td>Xiao-Cai-hu-Tang (Ohnishi et al., 2002); combination of Aurantii Fructus Immaturus (Citrus aurantium L.) and Paeoniae Radix Alba (Paeonia lacti flora Pall.) (Fang et al., 2009)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Hepatic P-gp</td>
<td>Quercetin (Bansal et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>Other hepatic transporters</td>
<td>Salviae Militiorrhiza Radix Et Rhizoma (Salvia miltiorrhiza Bge.) (Wang &amp; Sweet, 2013)</td>
</tr>
<tr>
<td></td>
<td>Serum albumin binding</td>
<td>Tanshinone IIA in Salviae Militiorrhiza Radix Et Rhizoma (Salvia miltiorrhiza Bge.) (Liu et al., 2008)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic CYPs</td>
<td>Captidis Rhizoma (Captis chinensis Franch.) (Han et al., 2011); Schisandrae Chinensis Fructus [Schisandra chinensis (Turcz.) Baill.] (Lai et al., 2009); Ginkgo Folium (Ginkgo biloba L.) (Tang et al., 2009a)</td>
</tr>
<tr>
<td></td>
<td>Hepatic UGTs</td>
<td>Ginkgo Folium (Ginkgo biloba L.) (Mohamed &amp; Frye, 2010); Evodiae Fructus [Evodia rutaecarpa (Juss.) Benth.] (Ueng et al., 2002b)</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal transporters</td>
<td>Rhe Radix et Rhizaoma (Rheum palmatum L.) (Wang et al., 2013); Gui Zhi Fu Ling Wan and Chia Wei Hisao Yao San (Lin et al., 2012)</td>
</tr>
</tbody>
</table>

ound, with each active compound having similar or different effects on the pharmacokinetics of the victim drug (Foti et al., 2007; Izzo, 2005); (4) HDIs can lead to severe (Bilgi et al., 2010) and even fatal (Chiang et al., 2005; Kupiec & Raj, 2005) ADRs; and (5) an increasing number of preclinical and clinical HDIs have been documented.

Traditional Chinese medicine (TCM) has a long history of medical use in China and is still used globally (Sucher, 2013). Despite the extensive number of reports on TCMs and HDIs, the findings on TCM-derived HDIs are frequently conflicting and puzzling. For example, Ginkgo Folium (Ginkgo biloba L.) interacted with warfarin, eventually leading to intracerebral hemorrhage in a patient (Matthews, 1998), perhaps due to the inhibitory effects of Ginkgo Folium (G. biloba L.) on cytochrome P450 enzymes (CYPs) (Gaudineau et al., 2004). However, other clinical studies indicated that oral treatment with Ginkgo Folium (G. biloba L.) extract did not alter the pharmacokinetics (Jiang et al., 2005) or pharmacodynamics of warfarin (Bal Dit Sollier et al., 2003). Such conflicting reports are misleading and present a big challenge in HDI research; furthermore, the conflicting findings are likely the result of complicated and multifaceted causes. Therefore, in the present review, based on searches of Medline, EBSCO, Science Direct and Web of Science using keywords, including traditional Chinese medicine, herb, herb–drug interaction, herbal–drug interaction and drug–drug interaction, and specific searches performed using the common and scientific names of particular TCMs, we summarize the TCM-derived pharmacokinetic HDIs that were reported from 1990 to 2015 and discuss the underlying mechanisms. In addition, the causes of the conflicting reports on TCM-derived HDIs are discussed and rational study designs for HDI research are proposed.

It should be noted that only HDIs derived from TCMs are reviewed in this article, whereas some extensively studied herbs such as black cohosh (Actaea racemosa L.) (Huang et al., 2010) and goldenseal (Hydrastis canadensis L.) (Chatterjee & Franklin, 2003) are excluded since they are not recorded in the Pharmacopoeia of People’s Republic of China (2010). St. John’s wort (Hypericum perforatum L.), called Hyperici Perforati Herba in TCM, is one of the most studied herbal medicines, thus we refer readers to related literature (Borrelli & Izzo, 2009; Di et al., 2008; Zhou & Lai, 2008). Furthermore, the TCM name plus the related Latin name of the plant source, which were revised according to the Pharmacopoeia of People’s Republic of China (2010), were applied for each TCM regardless of the names used in the literature. For example, the literature uses ginkgo or G. biloba (Bal Dit Sollier et al., 2003; Chatterjee et al., 2005; Jiang et al., 2005), while here, we refer to it as Ginkgo Folium (G. biloba L.).

**Progress and mechanisms of TCM-derived HDIs**

In general, multiple mechanisms may underlie the HDIs for a specific drug. TCMs cause pharmacokinetic interactions mainly by inhibiting or inducing drug-metabolizing enzymes and transporters, which are decisive for the absorption, distribution, metabolism and excretion (ADME) of victim drugs (Table 1). The roles of CYPs (Zhou et al., 2003) and p-glycoprotein (P-gp) (Marchetti
et al., 2007) in TCM-derived HDIs have been thoroughly discussed. Multiple studies have shown that the activity and expression of both CYPs and P-gp can be modulated by xenobiotics such as TCMs via various nuclear receptors (Bauer et al., 2008; Cerveny et al., 2007; Handschin & Meyer, 2003; Miller et al., 2008; Synold et al., 2001), which eventually change the in vivo disposition and pharmacokinetic properties of their substrates. Furthermore, functional coupling exists between CYPs and P-gp (Yasuda et al., 2002). P-gp can work in concert with metabolizing enzymes and play a role in drug metabolism. For example, P-gp influences the extent of drug metabolism in the intestines by prolonging the access of drugs to CYP3A4 near the apical membrane and by decreasing transport across the cells (Cummins et al., 2002, 2003). This dynamic interplay between intestinal P-gp and CYPs also contributes to the variability in the extent of drug interactions in humans (Yasuda et al., 2002). The effects of TCMs on CYPs, P-gp and the pharmacokinetics of victim drugs are summarized in Tables 2–4, respectively.

In addition to CYPs and P-gp, there are other drug metabolizing enzymes and transporters, although these have historically attracted less attention mostly due to the lack of validated systems and lower incidences of interactions (Williams et al., 2004). However, it should be noted that these drug-metabolizing enzymes and transporters are being documented in TCM-derived HDIs with increasing frequency. Studies on these enzymes and transporters are becoming more convenient to perform due to the development of validated testing systems (International Transporter Consortium, 2010; Zhang et al., 2009).

One of the enzymes that have attracted a large amount of attention is uridine 5′-diphospho-glucurono-syltransferases (UGTs), which catalyzes the conjugation of endogenous substances (e.g. bilirubin) and exogenous compounds (e.g. drugs) (Rowland et al., 2013). Given that glucuronidation is one of the major detoxification pathways, UGT impairment may lead to toxicological consequences (Grancharov et al., 2001). These enzymes can be modulated by many TCMs or their constituents such as *Evodiae Fructus* (*Evodia rutaecarpa* [Juss.] Benth) (Ueng et al., 2002b), *Ginkgo Folium* (G. *biloba* L.) (Mohamed & Frye, 2010), *Glycyrrhizae Radix et Rhizoma* (Glycyrrhiza uralensis Fisch.) (Moon & Kim, 1997), *Scutellaria Radix* (Scutellaria baicalensis Georgi) (Ueng et al., 2000), *Silybi Fructus* (Silybum marianum [L.] Gaertn.) (Venkataramanan et al., 2000), *Taraxaci Herba* (Taraxacum mongolicum Hand.-Mazz.) (Maliakal & Wanwimolruk, 2001), celastrol (Zhang et al., 2012), deoxyschizandrin and schisantherin A (Liu et al., 2012b), ginsenosides (Fang et al., 2013), which can eventually lead to significant interactions.

Transporters like organic anion-transporting polypeptide (OATP) may be involved in DDIs, which can lead to marked changes in the systemic drug exposure level and produce severe ADRs (Konig et al., 2013). Therefore, the HDI potential of hepatic OATP substrates including statins should be evaluated, as their hepatic pathway is significant (Elsbey et al., 2012). For instance, baicalin in *Scutellaria Radix* (*S. baicalensis* Georgi) reduced the plasma concentration of rosvuastatin in an OATP1B1-dependent manner (Fan et al., 2008); moreover, the extracts of *Rubi Fructus* (*Rubus chingii* Hu) and *Ginkgo Folium* (G. *biloba* L.) (Fuchikami et al., 2006) inhibited drug transporters like OATP-2B, while some flavonoids in TCMs demonstrated the ability to modulate OATP1B1-mediated (Wang et al., 2005) transport.

The solute carrier 22 family of transporters includes the organic cation transporters (OCTs), the organic anion transporters (OATs) and the organic cation/carnitine transporters (Konig et al., 2013). The HDI potential of OAT and OCT substrates should be examined, as their renal active secretion is important (Huang et al., 2007). Studies showed that some flavonoids in TCMs have the potential to modulate OCT (Ofer et al., 2005) transport, while components of the herbal medicine *Salviae Miltiorrhizae Radix Et Rhizoma* (*Salvia miltiorrhiza* Bge.) including lithospermic acid, rosmarinic acid, salvianolic acid A, salvianolic acid B and tanshinol inhibited the activity of hOAT1/hOAT3 (Wang & Sweet, 2013).

The physicochemical influences of TCMs on the intestinal absorption of drugs should not be ignored. Unlike modern drugs, TCMs are usually administered orally in the form of a decoction (Sucher, 2013), with each dose containing at least 100 mL of the decoction. It was reported that over 80% of the pH values of the water extracts of the tested TCMs (131 kinds) were from 4 to 6, while some pH values were lower than 3 or higher than 7 (Dong & Wu, 1989). It was reasonable to assume that the pH of the swallowed TCMs would influence the pH of the gastrointestinal tract. On the other hand, some TCMs inhibit the secretion of gastric acid (Satoh et al., 2000), which can also change the pH of the gastrointestinal tract. The passive absorption of the co-administered drug is likely to be influenced by a change in its ionization degree, which may be induced by a change in the pH of the gastrointestinal tract. On the other hand, the activities of some transporters like OATP that are expressed at the apical membrane of human epithelial cells in the small intestine are pH-sensitive (Kobayashi et al., 2003; Nozawa et al., 2004). Therefore, changes in the pH of the gastrointestinal
Table 2. Effects of the extracts and constituents of TCMs on CYPs.

<table>
<thead>
<tr>
<th>TCMs (plants)</th>
<th>Tested materials</th>
<th>Enzymes</th>
<th>Effects</th>
<th>Test systems</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrographis Herba</td>
<td>Extract; andrographolide</td>
<td>CYP2C, 3A4</td>
<td>↓</td>
<td>Rats; rat and human hepatocytes</td>
<td>Pekthong et al. (2009)</td>
</tr>
<tr>
<td>[Andrographis paniculata (Burm. F.) Nees]</td>
<td>Andrographolide and 14-deoxy-11; 12-didehydroandrographolide</td>
<td>CYP1A2, 2D6, 3A4</td>
<td>↓</td>
<td>HepG2 cells</td>
<td>Ooi et al. (2011)</td>
</tr>
<tr>
<td>Angelicae sinensis Radix</td>
<td>Ethanol extract</td>
<td>CYP2C19</td>
<td>↓</td>
<td>rhCYPs</td>
<td>Pan et al. (2011)</td>
</tr>
<tr>
<td>[Angelica sinensis (Oliv.) Diels]</td>
<td>Extract</td>
<td>CYP 1A2, 3A1</td>
<td>↑</td>
<td>Rats</td>
<td>Li et al. (2008)</td>
</tr>
<tr>
<td>Angelicae dahuricae Radix</td>
<td>Extract</td>
<td>CYP2C, 2D1, 3A</td>
<td>↓</td>
<td>RLMs</td>
<td>Ishihara et al. (2000)</td>
</tr>
<tr>
<td>Astragalus membranaceus (Fisch.) Bge. Var. mongholicus (Bge) Hsiao</td>
<td>Ethanol and dichloromethane extracts; Asiatic acid; Madecassic acid</td>
<td>CYP2C9</td>
<td>↓</td>
<td>rhCYPs</td>
<td>Pan et al. (2010)</td>
</tr>
<tr>
<td>Berberinea CYP3A4</td>
<td>↓</td>
<td>LMs</td>
<td>Yu et al. (2014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coptidis Rhizoma (Coptis chinensis Franch.)</td>
<td>Extract</td>
<td>CYP1A2, 3A1</td>
<td>↑</td>
<td>Rats</td>
<td>Li et al. (2008)</td>
</tr>
<tr>
<td>Berberine</td>
<td>CYP1A1</td>
<td>↓</td>
<td>HepG2 cells</td>
<td>Vrzal et al. (2005)</td>
<td></td>
</tr>
<tr>
<td>Berberine</td>
<td>CYP1A2, 2E1</td>
<td>↓</td>
<td>Rats; RLMs</td>
<td>Zhao et al. (2008)</td>
<td></td>
</tr>
<tr>
<td>Berberine</td>
<td>CYP1A2, 2D6, 3A4</td>
<td>↓</td>
<td>rhCYPs</td>
<td>Zhao et al. (2015)</td>
<td></td>
</tr>
<tr>
<td>Extract; coptisine; epiberberine</td>
<td>CYP2D6</td>
<td>↓</td>
<td>HLMs</td>
<td>Han et al. (2011)</td>
<td></td>
</tr>
<tr>
<td>Corydalis yanhusuo (W. T. Wang)</td>
<td>Total alkaloid extract</td>
<td>CYP2E1, 3A1</td>
<td>↑</td>
<td>Rats</td>
<td>Yan et al. (2014)</td>
</tr>
<tr>
<td>Corydalis Rhizoma</td>
<td>CYP1A2</td>
<td>↓</td>
<td>Human</td>
<td>Chen et al. (2010)</td>
<td></td>
</tr>
<tr>
<td>Curcuma longa L.</td>
<td>Extract</td>
<td>CYP2C19</td>
<td>↑</td>
<td>Rats</td>
<td>Wang et al. (2014b)</td>
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<td>Curcuma Longa Rhizoma</td>
<td>Curcumin</td>
<td>CYP2A6</td>
<td>↑</td>
<td>Human</td>
<td>Chen et al. (2010)</td>
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<td>Euphorbiae Pekinensis Radix</td>
<td>Extract</td>
<td>CYP2C19</td>
<td>↑</td>
<td>Rats</td>
<td>Wang et al. (2014b)</td>
</tr>
<tr>
<td>[Euphorbia pekinensis Rupr.]</td>
<td>Methanol extract</td>
<td>CYP1A1, 1A2, 2B</td>
<td>↓</td>
<td>Mice</td>
<td>Ueng et al. (2002b)</td>
</tr>
<tr>
<td>Evodiae Fructus [Evodia rutaecarpa (Juss.) Benth.]</td>
<td>Aqueous extract</td>
<td>CYP1A2</td>
<td>↑</td>
<td>Mice</td>
<td>Ueng et al. (2001)</td>
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<td>Rutacearpine</td>
<td>CYP1A</td>
<td>↑</td>
<td>Mice</td>
<td>Ueng et al. (2002a)</td>
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<td>Rutacearpine</td>
<td>CYP1A2</td>
<td>↓</td>
<td>MLMS; HLMs</td>
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(continued)
<table>
<thead>
<tr>
<th>TCMs (plants)</th>
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<th>Enzymes</th>
<th>Effects</th>
<th>Test systems</th>
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<td>Rutaecarpine</td>
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<td>Rats</td>
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<td>Rutaecarpine</td>
<td>CYP1A, 2B</td>
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<td>Rutaecarpine</td>
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<td>HLMs</td>
<td></td>
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<tr>
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<td>Extract and flavonoidic fractions</td>
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<td>HLMs</td>
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<td>Ginkgo Folium (Ginkgo biloba L.)</td>
<td>Gardeniae Fructus</td>
<td>CYP3A</td>
<td>Rats</td>
<td>Rats</td>
<td>Kang et al. (1997)</td>
</tr>
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<td>Extract; geniposide</td>
<td>CYP3A</td>
<td>Rats</td>
<td>Rats</td>
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<td>Extract; bilobaide</td>
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<td>Rats</td>
<td>Rats</td>
<td>Yagi et al. (2003)</td>
</tr>
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<td>Rats</td>
<td>Rats</td>
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<td>Rats</td>
<td>Rats</td>
<td>Gaudineau et al. (2004)</td>
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<tr>
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<td>Rats</td>
<td>Rats</td>
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<td>rhCYPs; HLMs</td>
<td>Chang et al. (2002)</td>
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<td>HLMs</td>
<td>HLMs</td>
<td>Etheridge et al. (2007), Liu et al. (2006)</td>
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<td>Glycyrrhizae Radix et Rhizoma</td>
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<td>CYP1A1</td>
<td>Rats</td>
<td>Rats</td>
<td>Lee et al. (2007a)</td>
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<td>rhCYPs</td>
<td>Wang et al. (2014b)</td>
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<td>Rats; hepatocytes</td>
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<td>HLMs; rhCYPs; mice</td>
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↓, induction; ↑, inhibition.

HLMs, human liver microsomes; LMs, liver microsomes; RLMs, mouse liver microsomes; rCYPs, recombinant CYP enzymes; rhCYPs, recombinant human CYPs; RIMs, rat intestinal microsomes; RKMs, rat kidney microsomes; RLMs, rat liver microsomes; C15, a human lung adenocarcinoma cell line; H4IIE, a rat hepatoma cell line; HepG2, a human liver carcinoma cell line; LS174T, a human colon adenocarcinoma cell line; MCF-7, a human breast adenocarcinoma cell line; NCI-H322, a lung carcinoma cell line.

*Berberine is a bioactive constituent in several TCMs including Coptidis Rhizoma (Coptis chinensis Franch) and Phellodendri chinensis Cortex (Phellodendron chinense Schneid) .
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**Other alkaloids of TCMs**

| Dauricine; dl-tetrahydropalmatine; tetramethylpyrazine | Dauricine; daurisoline | Rh-123 | Intracellular accumulation↑ | Activity ↓ | BCECs | He & Liu (2002a) |

**Other constituents of TCMs**

| Artesunate; homoharringtonine; bufalin | Pentagalloylglucose; tannic acid | Daunorubicin | Intracellular accumulation↑ | Activity ↓ | KB-C2 cells | Kitagawa et al. (2007) |

**Other drugs tested**

| Ritonavir | Efflux ↓ | Activity ↓ | Caco-2 and MDR1-MDCK cells, Caco-2 cells | Patel et al. (2004) |
| Talinolol | Efflux ↓ | Activity ↓ | Caco-2 cells    | Ofer et al. (2005) |
| Daunomycin | Intracellular accumulation and cytotoxicity ↑ | Activity ↓ | MCF-7 and MDA435/LCC6 cells | Zhang & Morris (2003) |
| Irinotecan | Efflux ↓ | Activity ↓ | Caco-2 cells    | Bansal et al. (2008) |
| Doxorubicin | Intracellular accumulation and cytotoxicity ↑ | Activity, protein and mRNA expression ↓ | K562 and K562/A cells | Shen et al. (2008) |
| Talinolol | Efflux ↓ | Activity ↓ | Caco-2 cells    | Ofer et al. (2005) |
| Daunomycin | Intracellular accumulation and cytotoxicity ↑ | Activity ↓ | MCF-7 and MDA435/LCC6 cells | Zhang & Morris (2003) |
| Daunorubicin | Intracellular accumulation and cytotoxicity ↑ | Activity ↓ | MCF-7 and MCF-7/ADR cells | Chung et al. (2005) |
| Talinolol | Efflux ↓ | Activity ↓ | Caco-2 cells    | Ofer et al. (2005) |

**Test systems**

- Caco-2 and MDK1-MDCK cells
- Caco-2 cells
- MCF-7 and MDA435/LCC6 cells
- MCF-7 and MCF-7/ADR cells
- K562 and K562/A cells
- KB-C2 cells

**References**

- Patel et al. (2004)
- Ofer et al. (2005)
- Bansal et al. (2008)
- Shen et al. (2008)
- Chung et al. (2005)
- He & Liu (2002a, 2002b)
- Cao et al. (2004)
- Efferth et al. (2002)
- Kitagawa et al. (2007)

**Additional notes**

- Bcap37/Adr, a multi-drug resistance variant of the human breast cancer cell line Bcap37; BCECs, the brain capillary endothelial cells; Caco-2, a human colonic carcinoma cell line; CCRF-CEM, a human T cell lymphoblast-like cell line; CEM/VLB100, CEM/E1000, CEM/ES000, multi-drug resistance variants of the human T cell lymphoblast-like cell line; CCRF-CEM; HCT15, a human colon carcinoma cell line; Hela, a human epithelial carcinoma cell line; HepG2-DR, a multi-drug resistance variant of the human hepatocellular liver carcinoma cell line HepG2/; K562/ADR, a multi-drug resistance variant of the human erythroleukemia cell line; K562/Adr, a multi-drug resistance variant of the human leukemic cell line K562; KB-C2, a multi-drug resistance variant of the human epithelial tumor cell line KB; KBv200, a multi-drug resistance variant of the human epithelial tumor cell line KB; MCF-7/Adr, a multi-drug resistance variant of the breast cancer cell line MCF-7; MDA435/LCC6, a human estrogen receptor-negative breast cancer cell line; MDR1-MDCK, an multi-drug resistance gene 1-transfected madin darby canine kidney cell line; MES-SA/DX5, a drug resistance variant of the rat uterine sarcoma human cell line; MOLT-4/DNR, a multi-drug resistance variant of the human acute lymphoblastic leukemia cell line MOLT-4; rBMECs, the rat brain microvesSEL endothelial cells; SGC7901/VCR, a variant of the human gastric cancer cells line, SGC7901; Rh-123, rhodamine 123.
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<td>Schisandrae Sphenantherae Fructus (Schisandra sphenanthera Rehd. et. Wils.)</td>
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*Quercetin is a constituent in lots of TCMs, such as Glycyrrhiza Radix et Rhizoma (Glycyrrhiza uralensis Fisch.).

Table 4. Continued

$\uparrow$, increased; $\downarrow$, decreased; $\rightarrow$, unchanged; i.g., intragastric administration; i.v., intravenous injection; p.o, oral administration; AUC, area under concentration–time curve; CL, clearance rate; $C_{\text{max}}$, maximum plasma concentration; $F$, bioavailability; $K_{p}$, absorption rate constant; MRT, mean residence time; $V_{d}$, volume of distribution; $t_{1/2}$, elimination half-life; $t_{1/2a}$, distribution half-life; $t_{1/2b}$, elimination half-life; PXR, pregnane X receptor; TCM, traditional Chinese medicine.

Quercetin is a constituent in lots of TCMs, such as Glycyrrhiza Radix et Rhizoma (Glycyrrhiza uralensis Fisch.).
tract may also influence the active absorption of co-administered drugs.

In addition, the inherent pharmacological effects of TCMs can influence the pharmacokinetics of victim drugs. TCMs may influence the pharmacokinetics of the victim drugs by modulating gastric emptying (Fang et al., 2009; Ohnishi et al., 2002) and competing for serum albumin binding (Liu et al., 2008). In addition, some toxic TCMs may affect the elimination of victim drugs by impairing renal (Grollman et al., 2007) and/or liver (Teschke et al., 2014) function.

Collectively, many TCM-derived HDIs have been reported, and these HDIs may occur at any step in the ADME of drugs. Although CYP and P-gp modulations are the main mechanisms underlying TCM-derived HDIs, other mechanisms should also be considered.

### Causes of conflicting reports

Despite the large numbers of reports on TCM-derived HDIs, the results are frequently conflicting, which can be confusing and misleading and they often fail to predict the magnitude or clinical significance of the HDIs. After a careful and systematic review of these reports, we classified the causes of the conflicting results into three categories: (1) complicated nature and poor quality control of TCMs, (2) different responses of the test systems to TCM exposure and (3) diverse study designs. Below, we discuss each of these causes in turn.

#### Complicated nature and poor quality control of TCMs

Unlike modern medicine, which consists of known compounds administered in specific doses, TCMs are usually derived from plants and are used as the crude extract of the herbs. The origin and application methods contribute to the complicated nature and difficulties in controlling the quality of TCMs.

For example, the use of homonyms and synonyms is very popular for TCMs due to their source complexes (Zhong et al., 2009). Here, the word homonyms means that plants which belong to different families or genera are used as the same TCM, while the word synonyms means that plants which share similar common name are used as different TCMs. In terms of homonyms, a good example is that the roots of the plants *Rheum palmatum* L., *Rheum tanguticum* Maxim et Balf and *Rheum officinale* Baill are all used as the TCM *Rhei Radix et Rhizoma*. As for synonyms, the TCM *Ginseng Radix et Rhizoma* only refers to *Panax ginseng* C. A. Mey. (Asian ginseng), while other ginsengs such as *Panax quinquefolium* L. (North American ginseng) and *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. (Siberian ginseng) are excluded. Plant subfamilies may differ from each other in terms of their HDI potential. For example, *P. quinquefolium* L. (North American ginseng) was 45-times more potent than *P. ginseng* C. A. Mey. (Asian ginseng) at inhibiting CYP1A2 (Chang et al., 2002), while *E. senticosus* (Rupr. et Maxim.) Maxim. (Siberian ginseng) at the generally recommended dosages do not influence drug-metabolizing enzymes such as CYP2D6 and CYP3A4 (Donovan et al., 2003). The conflicting terminology and results mentioned above can easily confuse readers who do not have basic knowledge of TCMs.

Moreover, the contents of the bioactive compounds in a TCM vary according to the cultivation area, harvest time, storage conditions and processing cycle of the plant (Chang et al., 2006b). For example, the concentrations of ginsenosides and eleutherosides showed a 15- to 200-fold variation in 25 available ginseng products (Harkey et al., 2001). Different batches of *Scutellaria Radix* (*S. baicalensis* Georgii) differ from each other in both chemical composition and bioactivity (de Boer et al., 2005). Thus, variations in the active constituents can lead to conflicting observations in HDI studies.

Another factor is that different extraction methods can lead to different overall HDI potentials. Unlike pure drugs, TCMs contain many constituents. The compounds in a TCM differ from each other quantitatively and qualitatively. Different extraction methods can lead to different extract ratios of the bioactive constituents of a TCM, thereby changing the overall interaction potential of the TCM. For example, the extracted flavonoidic fraction of *Ginkgo Folium* (*Ginkgo biloba* L.) inhibits CYPs more strongly than does the terpenoidic fraction (Gaudineau et al., 2004). Moreover, there are mouse CYP1A, CYP2C and CYP3A inducing agents in the ethyl acetate extract, but not in the aqueous extract, of *Salviae Miltiorrhizae Radix Et Rhizoma* (*S. miltiorrhiza* Bge.) (Kuo et al., 2006). The ethanol and dichloromethane extracts of *Centella asiatica* (L.) Urb. significantly inhibit cDNA-expressed human CYP2C9, however the aqueous and hexane extracts do not show these same effects (Pan et al., 2010). Studies also show that the methanol and aqueous extracts of *Evodiae Fructus* [*E. rutaecarpa* (Juss.) Benth] affect the activities of different drug-metabolizing enzymes (Ueng et al., 2002b). The metabolic interactions between the active constituents in TCMs like *Coptidis Rhizoma* (*Coptis chinensis* Franch.) make the potential HDIs more complicated (Liu et al., 2015).

Other quality problems including adulteration, misidentification, contamination, substitution of one herb with another and improper processing and preparation
may also explain the conflicting observations reported in HDI studies (Ko, 2004).

**Different responses of test systems to TCM exposure**

DDI studies are usually performed using various *in vitro* models (recombinant CYPs/UGTs, microsomes, cytosol, S9 fraction, cell lines, transgenic cell lines, primary or cryopreserved hepatocytes, liver/kidney slices and perfused liver/kidney) (Brandon et al., 2003). Animal studies, clinical case reports and clinical studies in man are also widespread reported. Early in the drug discovery process, the interaction potential of a compound is always evaluated *in vitro* through experiments that primarily investigate the metabolic stability and CYP inhibition/induction abilities of the compound. Hopefully, the data from *in vitro* assays could be used to predict *in vivo* especially clinical pharmacokinetics (Houston & Galetin, 2008). The strategy was also adopted in HDI studies.

However, the results of *in vivo* experiments and the results of *in vitro* studies are not always the same. For example, in contrast to the observed *in vitro* inhibition of CYP2C9, no interactions between *Ginkgo* Folium (*G. biloba* L) extract and CYP2C9 probe substrates were observed *in vivo* (Mohutsky et al., 2006). Moreover, *Ginkgo* Folium (*G. biloba* L) extract showed inductive effects on CYP2B *in vivo* but inhibitory effects *in vitro* (Umegaki et al., 2002). Silibinin, one of the constituents in *Silybi Fructus* (*S. marianum* [L.] Gaertn.), inhibits CYP3A4 *in vitro* but not *in vivo* (Fuhr et al., 2007). Rutacearpine, one of the main alkaloids in *Evodiae Fructus* (*E. rutaecarpa* [Juss.] Benth), induced both CYP1A1 and CYP1A2 *in vivo* (Lee et al., 2004; Ueng et al., 2001, 2005) but inhibited CYP1A2 in both mouse and human liver microsomes (Iwata et al., 2005; Ueng et al., 2002a). The inhibitory effects of DA-9801 (a mixed extract of *Dioscoreae Rhizoma* [*Dioscorea opposita* Thunb.] and *Dioscoreae nipponicae Rhizoma* [*Dioscorea nipponica* Makino]) on OCT1, OCT2 and OAT3 that were observed *in vitro* did not translate to *in vivo* HDIs in rats even at its maximum effective dose (Song et al., 2014).

The differences between *in vivo* and *in vitro* outcomes may be related to the *in vivo* metabolism of the herbs. For example, ginsenosides affect the *in vivo* activity of hepatic CYPs and drug transporters like P-gp via their intestinal metabolites after oral administration (Li et al., 2014a; Liu et al., 2006). In addition, *in vitro* test systems show more or less intrinsic drawbacks which were also associated with the inconsistent outcomes with *in vivo* studies (Brandon et al., 2003). For example, liver microsomes, the most widely used *in vitro* system for drug metabolism and inhibition studies, do not represent the true *in vivo* situation because they contain only the endoplasmic reticulum-localized enzymes, which means that interaction via other enzymes will not be detected with this system (Plant, 2004). The different responses of *in vitro* and *in vivo* test systems to TCM exposure suggest that the prediction of TCM-derived HDIs based on *in vitro* studies would be difficult and improbable (Andersson et al., 2004).

Interspecies variability (Bun et al., 2003), especially differences between primates and rodents (Richert et al., 2008), greatly influences the outcomes of *in vivo* interaction studies. Interspecies variability in drug-metabolizing enzymes (Gomez-Lechon et al., 2003) and drug transporters such as P-gp (Xia et al., 2006) and renal OATs and OCTs (Tahara et al., 2005) may contribute to the contradictory results in HDI studies. For example, the effects of *Ginkgo* Folium (*G. biloba* L.) extracts on the drug-metabolizing enzymes are specific to rats and should not be extrapolated to humans (Chatterjee et al., 2005).

Furthermore, the conflicting observations in HDI studies may be caused using different strains of a certain kind of animal. It was reported that tanshinone IIA isolated from *Salviae Miltiorrhizae Radix et Rhizoma* (*S. miltiorrhiza* Bge.) only induced CYP1A in C57BL/6J, but not DBA/2J, mice (Ueng et al., 2004). Strain-specific metabolizing capabilities (Komura & Iwaki, 2005; Tanoue et al., 2013) and transporter distribution (Soontornmalai et al., 2006) may be associated with the conflicting observations in HDI studies.

Sex also influences the outcomes. For example, *Sophorae Flavescentis Radix* (*Sophora flavescens* Ait.) extract only induced CYP2A and CYP3A in male C57BL/6Jarl mice, which was associated with the presence of certain compounds (Ueng et al., 2009). This phenomenon may be associated with sex-dependent hepatic CYP expression (Wolbold et al., 2003).

Age is another influencing factor, as age-related changes in the CYP responsivity to botanical supplementation exist (Gurley et al., 2005). The simultaneous and continuous intake of the *Ginkgo* Folium (*G. biloba* L.) extract significantly affects the hypoglycemic action of tolbutamide, particularly in aged rats (Sugiyama et al., 2004a).

Individual variability is another important factor that can cause problems in HDI research. Differential degrees of drug interactions may occur in individuals with variant forms of metabolizing enzyme genes such as CYP2C9 (Hummel et al., 2005). For instance, *Ginkgo* Folium (*G. biloba* L.) can induce omeprazole hydroxylation in a CYP2C19 genotype-dependent manner and
concurrently reduces the renal clearance of 5-hydroxyo-
meprazole (Yin et al., 2004).

Moreover, the foods, beverages, life-styles
Butterweck et al., 2004), and intestinal bacteria
Hasegawa, 2004) of the experimental subjects may also
influence the results of in vivo HDI studies.

Different responses of test systems to TCM exposure,
which are mainly caused by the expression levels and
patterns of specific drug metabolizing enzymes and
transporters, not only cause the conflicting results in
TCM-derived HDI studies, but also limit the ability to
predict the HDI potential in clinical settings based only
on in vitro studies or in vivo animal studies.

**Diverse study designs**

Diverse study designs cause different HDI results.
Factors that need to be considered in the study design
include, but are not limited to, the route of administra-
tion, dose, treatment period, choice of probe substrates
and solvent of the tested materials.

First, the administration route is important. For
instance, gastric infusion and intraperitoneal injection of
diallyl sulfide and diallyl disulfide from Allii Sativi Bulbus
(Allium sativum L.) show different activation profiles of
hepatic CYPs (Zhang et al., 2006). On the other hand,
the administration route of the victim drugs also influ-
ences the outcomes. For example, orally administered
Ginkgo Folium (G. biloba L.) extract only affects the
pharmacokinetics of orally, but not intravenously,
administered nifedipine in rats (Yoshioka et al., 2004).
Orally administered Zingiberis Rhizoma Recens
(Zingiber officinale Rosc.) juice significantly decreases the oral bio-
availability of cyclosporine; however, the pharmacokin-
etics of intravenous cyclosporine is not altered (Chiang
et al., 2006). This phenomenon may be related to the
different modulatory effects of a TCM on intestinal and
hepatic metabolism enzymes (Kinoshita et al., 2011; Lai
et al., 2009; van Waterschoot et al., 2009; Zhang et al.,
2007b). Most studies focus on hepatic metabolism; how-
ever, intestinal metabolism may be different from and
more important than hepatic metabolism after the oral administra-
ation of a drug (van Waterschoot et al., 2009).
Orally administered curcumin, a phenolic substance
from Curcumae Longae Rhizoma (Curcuma longa L.),
leads to the attenuation of the intestinal CYP3A level
but increases the hepatic CYP3A level in rats (Zhang et al.,
2007b). Moreover, the Schisandraceae Chinensis
Fructus (Schisandrae chinensis [Turcz.] Bail.) extract possesses
a more intensive modulatory effect on intestinal
CYP3A than on hepatic CYP3A (Lai et al., 2009). Given
that both TCMs and drugs are orally administered in
most cases, and that abundant drug metabolizing
enzymes and transporters are expressed in the intestine
and actively involved in the disposition of the oral
drugs, HDIs at intestinal sites would likely also be clinic-
ally relevant and should be examined carefully.

Second, the dose of the drug can affect the outcome.
Although TCMs usually exhibit dose-dependent induct-
ive (Deng et al., 2008a,b; Zhao et al., 2006) or inhibitory
(Gyamfi et al., 2000; Zuber et al., 2002) effects on CYPs,
they can sometimes have biphasic effects on CYPs, with
induction occurring at low dosages and inhibition
occurring at higher dosages (Hellum et al., 2009).
Occasionally, the dosages of the victim drugs also influ-
ence the outcomes. Pre-treatment with Andrographis
Herba (Andrographis paniculata [Burn. F.] Nees) extract
increases or decreases elimination at low or high dos-
ages of theophylline, respectively (Chien et al., 2010).
Altogether, these findings suggest that the dosage of a
TCM employed by a study should be carefully deter-
mined according to its clinical usage.

Another influencing factor is the treatment period of
the TCMs. Inductive effects usually occur after long-
term treatment. Schisandraceae Chinensis Fructus (S. chinen-
sis [Turcz.] Baill.) extract exerts inhibitory effects after
short-term treatment, but inductive effects after long-
term treatment on both hepatic and intestinal CYP3A
(Lai et al., 2009). Ginkgo Folium (G. biloba L.) usually
shows inhibitory effects on the metabolism of the co-
administered drugs (Ohnishi et al., 2003; Yoshioka et al.,
2004); however, long-term pre-treatment with this
extract induces hepatic metabolizing activity (Kubota
et al., 2004; Zhao et al., 2006). A single dose of
Glycyrrhiza Radix et Rhizoma (G. uralensis Fisch.) extract
does not affect the CYPs, while repeated treatment sig-
nificantly induces hepatic CYP3A and, to a lesser extent,
2B1 and 1A2 in male and female mice (Paolini et al.,
1998). Thus, choosing the appropriate treatment period
is critical.

Finally, for in vitro metabolism experiments, choosing
the appropriate probe substrates may be essential for
evaluating the effects on CYP3A4 (Galetin et al., 2003)
and CYP2C19 (Foti & Wahlstrom, 2008). Some extracts
[e.g. Ginkgo Folium (G. biloba L) (Yale & Glurich, 2005)]
or constituents [e.g. ginsenosides] (Hao et al., 2008) of
TCMs showed substrate-dependent effects on CYP3A4.
The effects were associated with the existence of mutual
and distinct substrate-binding domains for par-
ticular substrate subgroups within the CYP3A4 active
site (Galetin et al., 2003) and can yield inconsistent
results. The dose of the probe substrate also influences
the outcome (Xue et al., 2013). Furthermore, each of the
commonly used hydrophilic organic solvents, such as
acetonitrile, methanol, ethanol, 1-propanol, dimethyl
sulfoxide, N, N-dimethylformamide, polyethylene glycol
and propylene glycol, is not inert and has substrate-dependent effects on CYP3A4 activity (Iwase et al., 2006). For in vitro transport experiments, selection of the appropriate substrates, their concentrations, and the in vitro transport system are also critical when conducting in vitro interaction studies that involve individual liver OATP carriers (Noe et al., 2007).

Suggestions for designing future HDI studies

The fundamental cause of conflicting results in HDI studies is the lack of authoritative guidance. Although the current guidance document on DDIs can be consulted in HDI studies (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), due to the complicated and unique characteristics of herbal medicines, specific authoritative guides that provide recommendations for HDI studies are urgently needed. The aim of HDI studies is to assess the presence of HDI in a particular study, and generally to provide useful information for the avoidance of clinically significant HDIs. Therefore, the central rule in HDI studies should be the clinical relevance. Below, we propose some suggestions for how to appropriately design HDI studies based on this rule.

First, standardized manufacturing practices and reliable labeling information should be strictly implemented in the botanical supplement market to guarantee the quality of TCMs (Krochmal et al., 2004). Not only the name of the TCM, but also the Latin name of the plant should be clearly declared before publishing the HDI results.

Second, as for HDI studies on the crude extracts of TCMs, standard extraction methods should be used and strict quality control of the TCM extracts should be performed such as using the method based on the similarity of the chemical and bioresponse fingerprints among differently manufactured batches (Tilton et al., 2010). Given that most TCMs are clinically used as decoctions, aqueous extraction is more clinically relevant than other extraction methods.

Third, the test system should be carefully selected. The test system should be chosen based on the advantages and disadvantages of the different systems (Brandon et al., 2003). Basically, the selected systems should be reliable in predicting clinical HDIs from the obtained data. For example, human tissue and cell line-based systems should be used for in vitro (Jaiswal et al., 2014) studies, while the animal species that are the most similar to humans, especially humanized animals, are preferable for in vivo (Jaiswal et al., 2014; Katoh et al., 2008; Mitsugi et al., 2015; Sakamoto et al., 2015; Salphati et al., 2014) pre-clinical HDI studies. As for the study of crude TCM extracts, in vitro systems like hepatocytes and liver microsomes are not appropriate because not all of the constituents in the extract have access to the liver in in vivo situations due to the lack of absorption. Thus, testing the HDI potential of the non-absorbent constituents at hepatic site does not make sense.

Fourth, the study design should be elaborately developed. We refer readers to related literature (Bjornsson et al., 2003; International Transporter Consortium et al., 2010; Zhang et al., 2009) and guidance document on DDI studies (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf). It should be noted that the tissue exposure level rather than the plasma exposure level of the tested compound should be taken into account in concentration range selecting for in vitro studies. In the case of berberine, its hepatic exposure level was 70-fold higher than its plasma exposure level (Liu et al., 2010). For in vivo studies, the route of administration, dosage, treatment timing and duration and solvent of the tested materials should be strictly based on the clinical uses of the tested materials. For example, oral administration and multiple dosages for one to several weeks are preferred and the dosages of TCMs should be calculated from the clinical dosages based on body surface area.

Finally, the findings in terms of the potential risks and benefits for humans should be comprehensively interpreted. Given that TCMs contain various chemicals and bioactive compounds, the results of HDI studies that are based on the pure active constituents can only provide the HDI potential or possible mechanisms, while the overall HDIs of the TCM should be deduced from the results of in vivo studies that utilize the entire TCM rather than the individual compounds. Moreover, according to the current guidance document (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), conclusions could not be drawn based only on tests of significance and no effect boundary could be set between 80 and 125% for either the investigational herb medicine or the victim drugs used in HDI studies.

Future perspectives and conclusions

Due to quality and safety issues, including potential HDIs, it has been suggested that herbal medicines be restricted (Tirona & Bailey, 2006). However, we do not think that this is a rational choice. Given the remarkable curative effects of TCMs on various diseases and their long history of medical applications, the potential for HDIs is not a sufficient reason to persuade people to
stop using TCMs. First, most of the interactions result from a small number of prescription medications and the actual potential for harm is not serious (Peng et al., 2004; Sood et al., 2008). A review on the clinical evidence of herbal drugs as perpetrators of pharmacokinetic drug interactions has summarized that the available evidence indicates that, at commonly recommended doses, none of the popularly studied herbal drugs act as potent or moderate inhibitors or inducers of CYPs or P-gp (Hermann & von Richter, 2012). Second, the effects of the TCMs, such as *Ginkgo Folium* (*G. biloba* L.) extract (Sugiyama et al., 2004b), on drug-metabolizing enzymes can be rapidly recovered by discontinuing the TCMs, which suggests that serious interactions with drugs can be avoided by discontinuing the TCMs. Third, predictable HDIs may be intentionally used to increase the therapeutic effects or decrease side effects. For example, berberine from *Coptidis Rhizoma* (*C. chinensis Franch.*) markedly elevates the blood concentration of cyclosporine A (CsA) in renal-transplant recipients (Wu et al., 2005) by inhibiting hepatic and/or intestinal CYP3A4, increasing the emptying time of the stomach and small intestine (Xin et al., 2006) and inhibiting intestinal P-gp (Qiu et al., 2009), which allows the dosage of the expensive CsA to be reduced. Co-administration of *Schisandraceae Chinensis Fructus* (*S. chinensis* [Turcz.] Baill.) extract markedly increases the concentration of tacrolimus in the blood of patients with liver transplants, improves liver function and reduces the incidence of tacrolimus-associated side-effects (Jiang et al., 2010). Inhibition of P-gp at the blood-brain barrier is also helpful for improving the central nervous system distribution of drugs, which can increase its therapeutic effects (He & Liu, 2002a; Miller et al., 2008). Inhibiting P-gp function using *Glycyrrhizae Radix et Rhizoma* (*G. uralensis* Fisch.), *Rhei Radix et Rhizoma* (*R. palmatum* L.), *Poria* (*Poria cocos* [Schw.] Wolf.) and *Ephedrae Herba* (*Ephedra sinica* Stapf) increases paclitaxel sensitivity and enhances the clinical outcomes of chemotherapy for patients with cancer (Takara et al., 2005). More epidemiological studies similar to that by Zhang et al. (2011b) need to be performed to characterize the associations between clinical outcomes and the concomitant administration of herbal medicines.

Regardless, we should try to avoid harmful HDIs. Most importantly, specific authoritative guides that provide recommendations for HDI studies should be developed immediately. Quantitative assessments of the HDI potential and more clinically relevant research on an investigational drug should be performed so that the results can be used to predict whether dosage adjustments, prescribing modifications or other measures are needed to reduce risk and avoid undesired consequences. Furthermore, we should focus on educating the natural health product retailers and pharmacists about potential HDIs (Sim & Levine, 2010). Meanwhile, clinical risk management methods should be improved (De Smet, 2007; De Smet et al., 2008) and new computerized systems that are aimed at facilitating the process of data arrangement and drug interaction detection should be developed (Qian et al., 2010).

In addition to examining the influence of TCMs on co-administered therapeutic drugs, the effects of the co-administered drugs on the pharmacokinetics of TCMs should also be studied. For example, intestinal bacteria play an important role in the intestinal metabolism and absorption of glycoside constituents. Orally co-administered antibiotics can significantly influence the pharmacokinetics of glycoside constituents in TCMs (He et al., 2003). Some TCMs like *Coptidis Rhizoma* (*C. chinensis* Franch.) have a narrow therapeutic index (Ma et al., 2010), thus serious HDIs may also lead to safety issues of the TCMs.

Furthermore, most of the existing HDI studies are based on a single herbal medicine. However, in clinics, TCMs are usually used as a formula that consists of several herbs, which is believed to increase the curative effects and to reduce the side effects based on herb−herb interactions (Liu et al., 2013). It is reasonable to assume that herb−herb interactions make the integrated HDI potential of the formula more complicated, and thus the potential HDIs of the formula may be completely different from those of a single herbal medicine. Therefore, HDI studies based on TCM formulas should be reinforced.

In conclusion, many reports have documented that TCMs cause pharmacokinetic interactions with therapeutic drugs mainly by inhibiting or inducing drug-metabolizing enzymes and transporters. However, due to the complicated and unique nature of TCMs and diverse study designs, the results of these studies are conflicting, which makes them unreliable for clinical use. Here, we propose that a specific authoritative guide be established that provides recommendations for HDI studies, and indicate that it is important to optimize the design of the study based on the clinical relevance before performing related HDI studies.

**Declaration of interest**

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