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Review article:

CYTOCHROME P450 ENZYME MEDIATED HERBAL DRUG INTERACTIONS (PART 2)

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ABSTRACT

To date, a number of significant herbal drug interactions have their origins in the alteration of cytochrome P450 (CYP) activity by various phytochemicals. Among the most noteworthy are those involving St. John's wort and drugs metabolized by human CYP3A4 enzyme. This review article is the continued work from our previous article (Part 1) published in this journal (Wanwimolruk and Prachayasittikul, 2014). This article extends the scope of the review to six more herbs and updates information on herbal drug interactions. These include black cohosh, ginseng, grape seed extract, green tea, kava, saw palmetto and some important Chinese medicines are also presented. Even though there have been many studies to determine the effects of herbs and herbal medicines on the activity of CYP, most of them were *in vitro* and in animal studies. Therefore, the studies are limited in predicting the clinical relevance of herbal drug interactions. It appeared that the majority of the herbal medicines have no clear effects on most of the CYPs examined. For example, the existing clinical trial data imply that black cohosh, ginseng and saw palmetto are unlikely to affect the pharmacokinetics of conventional drugs metabolized by human CYPs. For grape seed extract and green tea, adverse herbal drug interactions are unlikely when they are concomitantly taken with prescription drugs that are CYP substrates. Although there were few clinical studies on potential CYP-mediated interactions produced by kava, present data suggest that kava supplements have the ability to inhibit CYP1A2 and CYP2E1 significantly. Therefore, caution should be taken when patients take kava with CYP1A2 or CYP2E1 substrate drugs as it may enhance their therapeutic and adverse effects. Despite the long use of traditional Chinese herbal medicines, little is known about the potential drug interactions with these herbs. Many popularly used Chinese medicines have been shown *in vitro* to significantly change the activity of human CYP. However, with little confirming evidence from clinical studies, precaution should be exercised when patients are taking Chinese herbal medicines concomitantly with drugs that are CYP substrates. Currently there is sufficient evidence to indicate that herbal drug interactions can occur and may lead to serious clinical consequence. Further clinical trial research should be conducted to verify these herbal drug interactions. Education on herbal drug interactions and communication with patients on their use of herbal products is also important.

Keywords: Herbal drug interactions, CYP, dietary supplements, herbal medicines, Chinese herbal medicines, drug interactions

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INTRODUCTION

Herbal medicines are increasingly being used as alternative medicines worldwide. As a result, it is very likely that some patients will take herbal medicines concomitantly with prescription or conventional medications. This may lead to unwanted adverse effects produced by herbal drug interactions. Many mechanisms underlying various herbal drug interactions have been suggested. However, the common mechanism for these interactions usually involved with a modulation of the absorption, metabolism, or elimination of co-administered drugs by the herb. Many herbs contain numerous phytochemical constituents which can induce or inhibit drug metabolizing enzymes such as cytochrome P450 (CYP) enzymes. As most clinically used drugs are metabolized by CYP enzymes, the changes in CYP activity initiated by herbal medications will alter the pharmacokinetics of the co-administered drugs. This subsequently will reduce the pharmacological effects of the co-administered drugs or cause toxicity (Gurley et al., 2002; Shi and Klotz, 2012). The systematic knowledge of herbal drug interaction, in particular on the level of drug absorption, metabolism, elimination and drug transport, may help to prevent adverse drug effects. For these reasons, evaluations of herbal drug interactions associated with drug metabolizing enzymes, especially CYP, are necessary to ensure the safety of the concomitant use of herbal medicines.

To continue from our previous review article (Part 1) published in this journal (Wanwimolruk and Prachayasittikul, 2014), the purpose of the current review is to present the available data on herbal drug interactions for the top six herbs (by sales) in the U.S. markets. These herbs included black cohosh, ginseng, grape seed extract, green tea, kava, and saw palmetto. Selected popularly used Chinese herbal medicines are also presented. They are Oriental herbs widely used in China, Korean and other Asian countries. These include Danshen (*Salvia miltiorrhiza*), Dong Quai (*Angelica sinensis*), Bai Hua She She Cao (*Oldenlandia diffusa*), Dang shen (*Codonopsis tangshen*) and Sheng Di Huang (*Rehmannia glutinosa*). These particular Chinese herbal medicines are known to have potential herbal drug interactions. In the following sections, this review article will provide some examples of herbal drug interactions occurred via mechanism based on modulation of human CYP.

Black cohosh

Black cohosh, known botanically as *Cimicifuga racemosa* L. (Family Ranunculaceae) is a shrub-like plant native to the eastern forests of North America. It has been used by Native Americans for menopausal symptoms such as hot flashes, premenstrual discomfort and dysmenorrhea (McKenna et al. 2001). Several preparations of black cohosh are available from drug stores, herbalists and traditional healers are highly recommended as a safe and effective natural remedy for menopausal symptoms. Black cohosh is ranked among the 10 top-selling dietary supplements in the United States (Gurley et al., 2012). Potential association between black cohosh and hepatotoxicity has been questioned in Australia, Canada and Europe. However, a recent meta-analysis of five randomized controlled clinical trials and a critical review suggested that black cohosh had no adverse effects on liver function (Shi and Klotz, 2012). Since the risks of hormone replacement therapy have become known, black cohosh preparations are now widely used among women seeking alternative treatments for menopausal illnesses (Mahady et al., 2003). Massive preclinical and clinical studies have presented contradictory evidence as regards effectiveness of black cohosh (Borrelli and Ernst, 2008). Early studies indicated that black cohosh extracts were effective in reducing the frequency and intensity of hot flashes among premenopausal and postmenopausal women (Borrelli and Ernst, 2008 and references herein; Frei-Kleiner et al., 2005; Wuttke et al., 2003). Whereas many trials showed no vasomotor symptom benefits (Borrelli and Ernst, 2008

and references herein; Geller et al., 2009; Liske et al., 2002). In view of the risks of hormone replacement therapy, many women will most likely continue to use black cohosh supplements. Therefore, the potential interactions between black cohosh supplements and prescription drugs remain clinically relevant.

Although black cohosh has been sold as a dietary supplement and an over-the-counter medication all over the world, its chemical components are not completely identified. While spiroketal triterpene glycosides are not phytoestrogens but they are thought to be responsible for the pharmacological activity of black cohosh (Li and Yu, 2006; Viereck et al., 2005). Most of commercial black cohosh products are currently standardized to triterpene glycosides, with 23-epi-26-deoxyactein (also recognized as 27-deoxyactein) which is the most abundant constituent (van Breeman et al., 2010). Another group of compounds isolated from black cohosh were polyphenolic derivatives. Thirteen compounds have been isolated from the rhizomes and roots of black cohosh (Nuntanakorn et al., 2006), including hydroxycinnamic acid derivatives (e.g., caffeic acid, ferulic acid, and isoferulic acid), fukiic acid ester derivatives (e.g., fukinolic acid and cimicifugic acids A and B), and piscidic acid ester derivatives (e.g., cimicifugic acids E and F).

Preclinical studies including *in vitro* and animals have investigated the effects of black cohosh or its extract constituents on human CYP activity. A study in mice has demonstrated that liver CYP3A11 enzyme was induced by 7-fold in mice treated with 500 mg/kg black cohosh for 28 days compared with the control group (Pang et al., 2011). In contrast, this induction effect was not found in the small intestine and kidney, suggesting that upregulation of mouse CYP3A11 by black cohosh was liver specific (Pang et al., 2011). It is interesting that mouse pregnane xenobiotic receptor (PXR) played an important role in the induction of CYP3A11; but human PXR was not activated by black cohosh. In addition, an *in vitro* study has shown that black cohosh extracts (75 % and 80 % ethanol) can inhibit many CYP isoenzymes including CYP1A2, CYP2C9, CYP2D6, and CYP3A4 (Huang et al., 2010). The triterpene glycosides appeared to be weak inhibitors (IC50 = 25-100 μM), while fukinolic acid and cimicifugic acids A and B were more potent inhibitors (IC50 = 1.8-12.6 μM) of all CYP isoenzymes studied. Therefore, these may have the potential to cause herbal drug interactions (Huang et al., 2010). However, it needs to realize that evidence of *in vitro* CYP inhibition, or that observed in animal models, may not exactly predict *in vivo* effects seen in humans (von Moltke et al., 1998).

For some clinical studies, single-time point phenotypic metabolic ratios were used to determine whether long-term supplementation of black cohosh (Cimicifuga racemosa) extract affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity (Gurley et al., 2005). Twelve healthy volunteers were randomly assigned to receive black cohosh for 28 days. Probe drug cocktails of midazolam and caffeine, followed 24 hours later by chlorzoxazone and debrisoquine, were administered before (baseline) and at the end of supplementation. Presupplementation and postsupplementation phenotypic trait measurements were determined for CYP3A4, CYP1A2, CYP2D6, and CYP2E1 by use of 1-hydroxymidazo-lam/midazolam serum ratios (1-hour sample), paraxanthine/caffeine serum ratios (6-hour sample), debrisoquine urinary recovery ratios (8-hour collection), and 6-hydroxychlorzoxazone/chlorzoxazone serum ratios (2-hour sample), respectively. Their results have shown that concomitant supplementation with black cohosh for 28 days did not affect the activities of human CYP1A2, CYP2E1 and CYP3A4. Black cohosh did not cause a statistically significant alteration in the pharmacokinetics of midazolam, indicating that black cohosh does not inhibit or induce CYP3A4. Thus, it is unlikely that black cohosh will cause any clinically important herbal drug interactions with drugs metabolized by CYP3A4 (Gurley et al.,

2005). However, black cohosh co-administration produced a statistically significant decrease in CYP2D6 activity. As the magnitude of inhibitory effect of black cohosh on CYP2D6 was only approximately 7% reduction, this may not be clinically relevant (Gurley et al., 2005). The authors concluded that black cohosh exhibited mild inhibition of CYP2D6; though, the clinical consequence of this effect remains uncertain. Later, the same group of investigators determined the effects of black cohosh supplementation on human CYP2D6 activity *in vivo* using debrisoquine as a specific CYP2D6 probe (Gurley et al., 2008a). The study was conducted together with other herbal supplements in 16 healthy volunteers. Subjects were randomized to receive black cohosh supplement for 14 days. The CYP2D6 substrate, debrisoquine (5 mg), was administered before and at the end of supplementation. Pre- and post-supplementation phenotypic trait assessments were determined for CYP2D6 using 8- hour debrisoquine urinary recovery ratios. Comparisons of pre- and post-supplementation results revealed no significant effect of black cohosh on the activity of CYP2D6 (Gurley et al., 2008a). Their results confirm previous clinical findings that black cohosh (Gurley et al., 2005) is not a potent modulator of human CYP2D6 *in vivo*. Thus, concomitant ingestion of black cohosh dietary supplements with drugs that are metabolized by CYP2D6 is not likely to cause clinically relevant herbal drug interactions (Gurley et al., 2008a). *In vitro* studies have provided inconsistent results with one reporting high (Ho et al., 2011), one moderate (Huang et al., 2010), and one no activity against CYP2D6 (Sevior et al., 2010). The discrepancy of *in vitro* and *in vivo* results again emphasizes caution in extrapolating findings of *in vitro* studies to clinical settings. It also suggested that there is need for clinical investigations to be pursued to confirm the *in vitro* findings. With respect to CYP1A2, clinical studies have also shown that black cohosh supplementation did not significantly alter the activity of human CYP1A2 (Gurley et al., 2005). Therefore, clinically important herbal drug interactions are unlikely to occur when black cohosh dietary supplements are concomitantly taken with drugs which are metabolized by CYP1A2.

With regard to effect of black cohosh on CYP3A4 activity, the *in vivo* results showing lack of effect were inconsistent with those found in an *in vitro* investigation which reported an inhibitory effect of black cohosh on CYP3A4 activity (Huang et al., 2010). Moreover, it has been shown by an *in vitro* study that certain triterpene glycosides isolated from black cohosh only weakly inhibited human CYP3A4 (Tsukamoto et al., 2005). This is in agreement with *in vivo* data suggesting no clinically significant interactions between black cohosh and CYP3A4 (Gurley et al., 2005, 2006).

Because hot flashes are the main indication for black cohosh use, women who experience this side effect of tamoxifen may decide to use black cohosh as a presumably safe remedy. With this reason, Li et al. (2011) carried out an *in vitro* study using human liver microsomes to examine the effect of black cohosh supplements on the activities of CYP enzymes involved in the metabolism of tamoxifen. Pharmacological activity of tamoxifen is dependent on the metabolic conversion into active metabolites by the action of CYP2D6 and CYP3A4. The objective of this study was to evaluate whether black cohosh extracts can inhibit formation of active tamoxifen metabolites and possibly reduce its clinical efficacy (Li et al., 2011). Using midazolam and dextromethorphan as probe substrates, ethanolic extract of black cohosh inhibited CYP3A4 and CYP2D6 with IC50 values of 16.5 and 50.1 μg/ml, respectively. The results of this study suggest that co-administration of black cohosh with tamoxifen might interfere with the clinical efficacy of this drug. However, additional clinical studies are required to understand the clinical significance of these *in vitro* results.

Taken together, the effect of black cohosh extract on the activity of human CYP enzymes has been evaluated in a number of clinical trials. The existing data indicate that black cohosh is unlikely to affect the pharmacokinetics of conventional drugs which are metabolized by CYP1A2, CYP2D6, CYP2E1 and CYP3A4. Moreover, Wanwimolruk and co-workers (Wanwimolruk et al., 2009; Wanwimolruk and Prachayasittikul, 2012) also found that seven different brands of commercial black cohosh products did not affect human CYP activities (CYP1A2 and CYP3A4) using an *in vitro* liver microsomal technique. Overall, black cohosh appears to present only minor risks in patients who are currently taking prescription drugs. Nevertheless, additional studies in humans are desirable to establish the safety of concomitant use of black cohosh and conventional drugs.

Ginseng

Ginseng, one of the most popular herbal medicines, it has been used for thousands of years in various Asian countries. In the last twenty years, ginseng has also been in demand in the Europe and United States as a dietary supplement (Qi et al., 2011). Today ginseng products rank among the most commonly used herbal products. Ginseng is the 5th best-selling herb in the United States (Goey et al., 2013). Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are the two most well-known ginseng herbs worldwide (Qi et al., 2011).

P. ginseng is one of the twenty most frequently used complementary alternative medicines (CAM) in use by cancer patients (Werneke et al., 2004). *P. ginseng* is believed to possess anti-neoplastic, anti-aging, anti-oxidative and immunomodulatory effects (Goey et al., 2013). This herb is used for cancer prevention, erectile dysfunction, improved cognitive functions and enhanced physical functions (Goey et al., 2013). *P. ginseng* consists of ginsenosides and sapogenins, of which ginsenosides are the main components. Some notable differences between ginseng species exist in relation to the content and composition of ginsenosides, a factor that may be connected with a differential drug interaction potential. The recommended daily dose of *P. ginseng* is 200 mg of standardized (i.e., 4 % total ginsenosides) extract.

Several *in vitro* studies have investigated the effects of ginseng extracts or its extract constituents on CYP enzymes using various techniques. These *in vitro* studies have shown that ginseng has potential to inhibit CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Foster et al., 2003). However, these results have been mainly inconsistent and even conflicting (Hermann and von Richter, 2012; Shi and Klotz, 2012). Purified constituent kaempferol from ginseng displayed significant inhibition of CYP3A4 activity, similarly P-gp (P-glycoprotein)-mediated efflux of ritonavir was also significantly inhibited (Patel et al., 2004). A major problem with the *in vitro* experiments is that the concentrations required to produce CYP inhibition or induction *in vitro* were often extremely high and unlikely to be attained *in vivo* following recommended doses of herbal products (An and Morris, 2010). Therefore, reliable predictions of the *in vivo* relevance of these findings are unachievable in practical terms.

Even though there are so many *in vitro* studies have been conducted, clinical studies of pharmacokinetic ginseng drug interactions are limited. The majority of *in vitro* studies demonstrated that ginseng competitively inhibits human CYP3A4. Thus, the effect of ginseng would have on CYP3A4 could be anticipated in the clinical studies. A number of clinical studies did find significant inhibition of CYP3A4 by ginseng when they used midazolam as a typical marker for human CYP3A4 enzyme. The effect of *P. ginseng* on the activities of CYP enzymes was investigated in a single time-point phenotyping study. Caffeine was used as a specific probe for CYP1A2, debrisoquine for CYP2D6, chlorzoxazone for CYP2E1, and midazolam for CYP3A4. The ginseng extract was given at a dose of 500 mg (three times daily, stand-

ardized to 5 % ginsenosides) for 28 days as a pretreatment. They found no significant effects of *P. ginseng* on the activities of all CYP enzyme studied including CYP1A2, CYP2D6, CYP2E1 and CYP3A4 (Gurley et al., 2002). A similar study was conducted in healthy elderly subjects, using the same dose of *P. ginseng* product, and treatment duration, as well as the same CYP probe drugs, *P. ginseng* supplementation had no significant effects on any CYP enzyme activity (Gurley et al., 2005). Presumably, the inhibitory potency of ginsenosides is too low to produce significant clinical CYP3A4 inhibition (Goey et al., 2013). High plasma concentrations of ginsenosides are required for inhibition of CYP3A4, as the IC50 values of many ginsenosides have shown to be more than 1000 times greater than the IC50 value of the potent CYP3A4 inhibitor ketoconazole (Henderson et al., 1999). Later reports by Anderson et al. (2003) supported the findings of Gurley and co-workers (Gurley et al., 2002, 2005) in respect to lack of ginseng on the activity of human CYP3A4. In Anderson and colleagues' study (Anderson et al., 2003), 100 mg of *P. ginseng* extract (standardized to 4 % ginsenosides) were given twice a day for 14 days to 20 healthy volunteers. The urinary 6-β-hydroxycortisol/cortisol ratio, a marker of CYP3A enzyme induction was found to remain unchanged after the ginseng supplementation. These results indicate that *P. ginseng*, at recommended doses, does not confer significant CYP3A induction *in vivo* (Anderson et al., 2003).

However, one clinical study, reported that *P. ginseng* caused a significant induction of CYP3A4 (Malati et al., 2012). Intake of 500 mg *P. ginseng* (twice daily for 28 days, standardized to 5 % ginsenosides) by healthy volunteers significantly decrease (34 %) the AUC of oral midazolam. This suggested that long term ginseng supplementation caused an induction of CYP3A4 enzyme. Remarkably, this significant induction of CYP3A4 differed from the observations found in the other two studies with midazolam, despite a similar composition of the *P. ginseng* product (500 mg extract, standardized to 5 % ginsenosides) and a lower dosing frequency. Perhaps, differences in determinations of CYP3A4 activity account for these conflicting results. A one-hour post dose serum concentration ratio of 1-hydroxymidazolam/ midazolam was the primary method used in studies indicating no apparent interaction between *P. ginseng* and midazolam (Gurley et al., 2002, 2005). Whereas midazolam AUC was assessed in the clinical study suggesting CYP3A4 induction by *P. ginseng* (Malati et al., 2012). It has been noted that determination of the AUC of midazolam is more accurate to assess CYP3A4 activity than a single sample collection of midazolam (Penzak et al., 2008). Thus, it is possible that a CYP3A4 induction by *P. ginseng* may have failed to notice in the studies with a single sampling strategy (Goey et al., 2013).

The effects of American ginseng (*Panax quinquefolius*) on the pharmacokinetics of the HIV protease inhibitor and sensitive CYP3A4 substrate indinavir were investigated in 14 healthy adults (Andrade et al., 2008). The HIV protease inhibitor, indinavir using 800 mg doses was administered three times a day, either alone or together with 1.0 g doses of American ginseng three times daily over 2 weeks period (dried whole root 500 mg capsules). The results have shown that American ginseng did not affect the pharmacokinetics of the CYP3A4 substrate indinavir. This suggests that American ginseng does not cause any appreciable CYP3A4 induction or inhibition.

The influence of a standardized Siberian ginseng (*Eleutherococcus senticosus*) extract on the activity of cytochrome P450 CYP2D6 and CYP3A4 was assessed in 12 healthy subjects (Donovan et al., 2003). Probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were administered orally at baseline and again following treatment with Siberian ginseng (1 x 485 mg twice daily) for 14 days. Urinary concentrations of dextromethorphan and dextorphan were quantified, and dextromethorphan metabolic ratios were determined at

baseline and after Siberian ginseng treatment. Likewise, plasma samples were collected (0–60 h) for alprazolam pharmacokinetics at baseline and after Siberian ginseng treatment to assess effects on CYP3A4 activity. There were no statistically significant differences between pre- and post-Siberian ginseng treatment in term of urinary dextromethorphan/dextrorphan metabolic ratios. This indicates a lack of Siberian ginseng effect on CYP2D6 enzyme activity. For alprazolam results, there also were no significant differences in plasma concentrations and derived pharmacokinetic parameters (Cmax, tmax, AUC, t1/2). These results indicate that Siberian ginseng does not induce or inhibit CYP3A4 enzyme. Their results are in line with the outcomes reported for *P. ginseng* preparations as described above. These also suggest that standardized extracts of Siberian ginseng at generally recommended doses for over-the-counter use are unlikely to affect the activity of CYP2D6 or CYP3A4. There appears to be little likelihood of significant herbal drug interactions between Siberian ginseng and drugs predominantly metabolized by CYP2D6 or CYP3A4 isoforms (Donovan et al., 2003).

The effects of *P. ginseng* on the pharmacokinetics and pharmacodynamics of warfarin were examined in 12 healthy subjects (Jiang et al., 2004). A single 25-mg dose of warfarin (Coumadin™, 5 × 5-mg tablets) was administered to each subject with and without pretreatment with multiple doses of Asian ginseng for 1 week (Korean ginseng, each capsule containing extract equivalent to 0.5 g Panax ginseng root and 8.93 mg ginsenosides as ginsenoside Rg1; 2 × 0.5-g capsules, three times daily). Dosing of ginseng was continued for a further 1 week after warfarin administration. The bioanalytics comprised enantiomer-selective quantification of S-warfarin, which is predominantly metabolized to S-7-hydroxy-warfarin by CYP2C9, and R-warfarin, which is metabolized by CYP3A4 and CYP1A2. This allows for a separate systematic assessment of any potential alteration of these metabolic pathways by concomitant *P. ginseng* treatment. The results have shown that *P. ginseng* treatment did not affect the pharmacokinetics and clearance of both warfarin enantiomers in human subjects. This implies that ginseng has no appreciable effect on the activity of CYP1A2, CYP3A4, or CYP2C9 in healthy subjects. Pharmacodynamic endpoints of warfarin were also evaluated in this study. It was shown that *P. ginseng* did not significantly alter blood coagulation (i.e., International normalized ratio, INR) outcomes and platelet aggregation (Jiang et al., 2004).

The lack of effect by ginseng on the pharmacokinetics of warfarin was largely ratified by the results obtained by the same group of investigators (Jiang et al., 2006). This study employed a similar study design for investigating warfarin interactions and was a comparable subject size (12 healthy male subjects). Similar as in the previous study, dosing of the herbal product was the same and continued for a further week after warfarin administration. The results demonstrated that concomitant administration of ginseng with warfarin did not affect the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin (Jiang et al., 2006). The pharmacodynamic endpoints of warfarin including International normalized ratio (INR) and platelet aggregation were not altered by treatment with ginseng. Therefore, these observations confirmed the findings resulting from previous study (Jiang et al., 2004).

A randomized, double-blind, placebo-controlled trial was conducted in healthy adult subjects, to evaluate the interactions between American ginseng and warfarin (Yuan et al., 2004). In this 4-week study, 20 subjects received warfarin for 3 days during weeks 1 and 4. Beginning in week 2, subjects were assigned to receive either American ginseng (*P. quinquefolius*, 0.5 g capsules) or placebo. INR and plasma warfarin level were determined. The peak INR was shown to decrease statistically significantly after 2 weeks of ginseng administration compared with placebo. The INR area under

the curve (AUC), peak plasma warfarin level, and warfarin AUC were also significantly reduced in the ginseng group as compared with the placebo group. The average group results, however, have to be interpreted with caution, because the INR data in the ginseng group were mainly pushed by one outlier subject exhibiting a high baseline INR (1.32) and an unusually increased peak INR after warfarin administration on day 4. After ginseng co-administration, the peak INR of this patient declined remarkably from 5.16 to 2.75, and the corresponding AUC of INR decreased from 17.5 to 11.1. Even though the authors pointed out that the results of their study remain statistically significant, when this outlier patient is excluded from analysis, it becomes apparent, that parallel group studies of such a small sample size are difficult to interpret (Hermann and von Richter, 2012).

Overall, the clinical studies on the effects of ginseng on the activity of human CYP yielded consistency of data which convincingly suggest that at recommended therapeutic doses, ginseng products have no significant effect on CYP enzyme either inhibitory or induction properties. Therefore, it is unlikely that herbal drug interactions will occur via CYP metabolism when the patients take ginseng products concomitantly with prescription drugs. Furthermore, the published data from clinical studies on ginseng and warfarin interaction suggest that high repeated doses of *P. ginseng* (over 1 week) did not significantly change the pharmacokinetics or pharmacodynamics of 25 mg warfarin single doses in healthy adults (Greenblatt and von Moltke, 2005; Jiang et al., 2004). On the other hand, Yuan et al. (2004) conducted a small parallel group study in healthy subjects which revealed conflicting findings. They employed a different warfarin dosage regimen (5 mg warfarin daily on 3 consecutive days) and a 2-week treatment with American ginseng (*P. quinquefolius*) at the high end of the recommended dose range. Their finding suggests American ginseng may reduce warfarin exposure (i.e., increases warfarin clearance), thus diminishing the anticoagulant effect of warfarin to a modest extent (Yuan et al., 2004). The differences in the outcome of these studies could be either due to different properties of Asian ginseng (*P. ginseng*) and American ginseng (*P. quinquefolius*) products, or differences in the study designs (1-week vs. 2-week treatments). Alternatively, the differences could be due to the limitations of the small parallel group study which was apparently highly influenced by an outlier subject (Hermann and von Richter, 2012; Yuan et al., 2004).

Grape seed extract

Grapes (*Vitis vinifera*) are one of the most consumed fruit in the world and grape seed extract is one of the top-selling herbal dietary supplements in the United States (Choi et al., 2011; Sparreboom et al., 2004). Polyphenolic compounds including flavonoids and resveratrol are well-known components of grapes. Approximately 90-95 % of grape polyphenols exist in grape seeds and grape skin. Most of the grape seed polyphenols are quite different from tea polyphenols. Grape seed polyphenols are mainly rich in polymers (e.g., procyanidins or proanthocyanidins) whereas most tea polyphenols are monomers, such as catechins. Various naturally occurring polyphenol antioxidants are known to be present in grape seeds commonly known as procyanidins (Bartolome et al., 1996; Singleton, 1992). Commercial preparations of grape seed polyphenols, widely referred to as “grape seed extract”, are standardized to contain 95 % procyanidins and are marketed in the USA as a dietary supplement. The consumer interest in grape seed extract has been mainly due to the high content of antioxidants in the form of procyanidins in this extract (Kaur et al., 2009). Many studies have shown that grape seed procyanidins possess anti-inflammatory, anti-arthritic and anti-allergic activities and prevent heart attack and skin aging (Bagchi et al., 1998; Maffei et al., 1996). Grape seed extract has been demonstrated to exhibit antioxidant and anticancer activities in both *in*

vitro and *in vivo* models (Bagchi et al., 2002; Kaur et al., 2009; Sharma et al., 2004; Ye et al., 1999). There are a number of studies suggesting that grape seed extract could be a potential cancer chemopreventive agent against various cancers in animal models (Bomser et al., 1999; Zhao et al., 1999). An epidemiological study has shown that increased consumption of grapes is associated with reduced cancer risk (Kaur et al., 2009; Zheng et al., 1993). Overall, completed studies from various scientific groups conclude that both grapes and grape-based products are excellent sources of various anticancer agents and their regular consumption should thus be beneficial to the general population (Kaur et al., 2009).

Wine consumption has been reported to have many beneficial health effects, and wine may also be a source of grape seed procyanidins (Halpern et al., 1998; Soleas et al., 1997). Epidemiological studies have strongly suggested that light to moderate wine consumption is associated with a reduced incidence of mortality and morbidity from coronary heart disease more than the consumption of other alcoholic beverages. This gave rise to what is now popularly known as the "French Paradox" (Renaud and De Lorgeril, 1992).

Resveratrol appeared to be an important constituent in grape seed extract. It has been studied extensively and evidence points to the potential of resveratrol for human health improvement (Choi et al., 2011). Red wine solids and resveratrol were investigated for their ability to alter human CYP activity. *In vitro* studies have shown that both red wine solids and resveratrol were irreversible (mechanism-based) inhibitors of CYP3A4 and non-competitive reversible inhibitors for CYP2E1 in microsomes from rat liver and cDNA-expressed CYP human liver cells (Chan and Delucchi, 2000; Piver et al., 2001). Resveratrol is an electron-rich molecule with two aromatic benzene rings linked by an ethylene bridge. Aromatic hydroxylation and epoxidation of resveratrol mediated by CYP3A4 possibly produce a reactive p-benzoquinonemethide metabolite which is highly capable of covalently binding to CYP3A4 enzyme. Consequently, this leads to inactivation of CYP3A4 (i.e., mechanism-based inhibition), and potential drug interactions (Rodríguez-Fragoso et al., 2011). Interestingly, inactivation of CYP3A4 by a range of red wines did not correlate with the content of resveratrol (Chan and Delucchi, 2000).

CYP1A1 and CYP1B1 have been shown to act as bioactivating enzymes for activation of carcinogens, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and benzo[a]-pyrene (Song et al., 2010). An *in vitro* finding revealed that grape seed extract was able to reduce CYP1A1 and CYP1B1 contents in breast cells exposed to NNK and benzo[a]pyrene (Song et al., 2010). It is possible that reduction of CYP1A1 and CYP1B1 contents may contribute to the ability of grape seed extract to suppress cellular acquisition of cancer-related properties induced by NNK and benzo[a]pyrene.

Chow and co-workers (Chow et al., 2010) carried out a clinical study to determine the effect of pharmacologic doses of resveratrol on drug- and carcinogen-metabolizing enzymes. Forty-two healthy volunteers underwent baseline assessment of CYP and phase II detoxification enzymes. CYP1A2, CYP2D6, CYP2C9, and CYP3A4 enzyme activities were assessed by the metabolism of caffeine, dextromethorphan, losartan, and buspirone, respectively. After the baseline evaluation, study participants received a pretreatment with 1 g of resveratrol once daily for 4 weeks. Enzyme assessment was repeated upon pretreatment completion. They found that 4 weeks of daily resveratrol administration resulted in a 16 % decrease in the caffeine/paraxanthine metabolic ratio. This suggests resveratrol pretreatment caused an induction of human CYP1A2 activity. Many environmental carcinogens, such as polycyclic aromatic hydrocarbons, are generally thought to be activated by the CYP1A and CYP1B subfamilies to form genotoxic epoxide metabolites, which

can bind to DNA, forming DNA adducts. Therefore, inhibition of these enzymes is thought to be an important mechanism in the prevention of carcinogenesis. Resveratrol pretreatment also resulted in 33 %, 70 %, and 171 % increases in buspirone AUC, metabolic ratio of dextromethorphan to dextrorphan, and metabolic ratio of losartan to E3174, respectively. These changes implied that resveratrol inhibited the activities of CYP3A4, CYP2D6, and CYP2C9, respectively (Chow et al., 2010). Among these CYP enzymes, CYP3A4 metabolizes the great majority of drugs, including immunosuppressive drugs for transplant patients, HIV protease inhibitors, cholesterol-lowering statin drugs, and chemotherapeutics. Inhibition of CYP3A4 would result in elevation of the systemic blood levels of drugs metabolized by this CYP3A4 isozyme, which could lead to increased drug toxicity (Chow et al., 2010). CYP2D6 is accountable for converting tamoxifen to the potent antiestrogen endoxifen. Studies have shown that individuals with decreased CYP2D6 metabolism due to genetic variations or enzyme inhibition have reduced plasma endoxifen concentration and increased risk of breast cancer relapse (Goetz et al., 2007; Jin et al., 2005). It is possible that resveratrol could reduce the formation of endoxifen, so affecting the chemopreventive or anticancer activity of tamoxifen. CYP2C9 is involved in the metabolic clearance of a wide variety of therapeutic drugs, including many non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, oral anticoagulants, and oral hypoglycemics. This raises the question of whether resveratrol would decrease the clearance of these drugs, probably intensifying the toxicity of these drugs (Chow et al., 2010). The authors conclude that resveratrol can modify enzyme systems implicated in activation and detoxification of carcinogens. This may be one mechanism by which resveratrol prevents carcinogenesis. However, pharmacologic doses of resveratrol could possibly directly enhanced adverse drug reactions or alter drug efficacy due to inhibition or induction of certain CYPs. Further clinical development of resveratrol for cancer prevention should reflect evaluation of lower doses of resveratrol to minimize adverse metabolic drug interactions (Chow et al., 2010). However, these speculations of consequence of resveratrol on drug efficacy and drug interactions have not been testified by clinical studies. It also needed to be cautioned that with these speculations as although the changes produced by resveratrol were statistically significant, but are relatively small according to current FDA drug interaction guideline recommendations (US Department of Health and Human Services/ Food and Drug Administration Center for Drug Evaluation and Research, 2012).

In addition, nine commercial brands of grape seed extract dietary supplements were tested *in vitro* to determine whether grape seed extracts can inhibit the activity of human CYP3A4 (Wanwimolruk et al., 2009). Their results have shown that grape seed extract had considerably little effect on CYP3A4 activity, ranging from 0 % (no effect) to 26.8 % inhibition. Thus, this suggests that the inhibitory effect on CYP3A4 caused by grape seed extract dietary supplements was mild but the effect was variable depending on the brand of the grape seed extract products. This magnitude of CYP3A4 inhibition by grape seed extract is rather small as compared with inter-individual variation of human CYP3A4 activity (Watkins 1994; Wrighton et al., 1993; Zhang et al., 1997). Therefore, it is doubtful that adverse herbal drug interactions will occur when grape seed extract dietary supplements are concomitantly taken with prescription drugs that are metabolized by CYP3A4.

Green tea

Green tea (*Camellia sinensis*, Family Theaceae) is made from the leaves of the plant Camellia sinensis Thaecae, and has been part of Eastern medicine for millennia. Tea was first used as a medicinal herb in ancient China and now tea is a widely consumed beverage. Second only to water, green

tea in particular, is the most popular beverage in the world, especially Asian countries. The potential preventive activities of green tea against cancer and cardiovascular diseases have been thoroughly investigated during the past 25 years (Yang and Pan, 2012). In addition to conventional green tea infusion, concentrated green tea extract in liquid or capsule formulations have become the vehicle of choice for healthy individuals seeking to increase their overall health. One of example is those being marketed for weight reduction. Other health claims for green tea, such as its supposed cardiovascular protection and anti-cancer effects (see critical reviews - Deka and Vita, 2011; Lambert et al., 2007; Moore et al., 2009; Sturgeon et al., 2009; Yang and Wang, 2011; Yang et al., 2011), have further contributed to the increasingly widespread consumption of large dosages of green tea extract. Cancer patients in particular may be desirous to self-medicate with such herbal supplements including green tea, in hopes of suspending the progression of their disease and/or ease the adverse effects associated with conventional chemotherapy. Epidemiological studies reveal that consumption of green tea reduces cancer risk (Dreosti et al., 1997; Katiyar and Mukhtar, 1996; Hayat et al., 2013). These data have been proved by the findings of numerous preclinical studies showing that green and black tea are potent inhibitors of carcinogenesis in various rodent models, including models for cancers of the skin, lung, esophagus, stomach, liver, duodenum, small intestine, pancreas, colon-rectum, and mammary gland (Bode and Dong, 2009; Yang et al., 1997, 2002).

The typical constituents in green tea are tea polyphenols known as catechins, caffeine and a unique amino acid (theanine). The health effects of the tea seem to be due to catechins which represent 30-45 % of solid green tea extract and have anti-cancer, anti-metastatic, anti-inflammatory, anti-anthrax lethal factor, and vasculoprotective properties (Schönthal, 2011; Yang and Pan, 2012). Like many drugs, these tea chemicals are absorbed, metabolized and eliminated. Therefore, potential interactions between tea constituents and drugs as competitive substrates or inhibitors can be anticipated. Tea catechins may perhaps directly bind to drugs and reduce their absorption, bioavailability and their biological activities. Tea catechins may also increase or decrease the activities of drug-metabolizing enzymes and drug transporters (Yang and Pan, 2012).

There are numerous in vitro data on the effects of green tea and green tea extract on the metabolism of drugs and activities of CYP. Many of these studies were in vitro studies and some were conducted in animals. As this review is aimed to provide information on herbal drug interactions in humans, these studies are not relevant and therefore are not included. One of important clinical studies is performed by Donovan et al. (2004) who determined the effect of decaffeinated green tea extract on the disposition of dextromethorphan (a CYP2D6 substrate) and alprazolam (a CYP3A4 substrate) in healthy volunteers. After 14-day pretreatment with two capsules twice daily of decaffeinated super green tea extract (containing 211 ± 25 mg of green tea catechins/capsule), the subjects received a single 30 mg dose of dextromethorphan and 2 mg of alprazolam. The results derived from the study revealed no significant alterations in the Cmax, tmax, AUC and elimination half-life (Donovan et al., 2004). The authors suggested that decaffeinated green tea is unlikely to alter the disposition of medications primarily dependent on the CYP2D6 or CYP3A4 pathways of metabolism.

Chow and colleagues (Chow et al., 2006) conducted a clinical study to determine the effect of repeated green tea catechin administration on human CYP enzyme activities. After refraining from tea or tea-related products for or 4 weeks, 42 healthy volunteers received a cocktail of CYP metabolic probe drugs, including caffeine, dextromethorphan, losartan, and buspirone for assessing the activity of CYP1A2, CYP2D6, CYP2C9, and CYP3A4, respectively. Blood and urine

samples before and 8 h after probe drug administration were collected to determine parent drug and metabolite concentrations for measurements of baseline CYP enzyme activities. After pretreatment with four capsules of green tea catechin extract (contains 800 mg epigallocatechin gallate [EGCG]) daily for 4 weeks, a single dose of a probe drug was coadministered to the volunteers and blood samples were collected in the same manner. Their results have demonstrated that 4-week pretreatment with green tea catechin did not alter the activities of CYP1A2, CYP12D6, and CYP12C9. However, green tea pretreatment resulted in a significant increase (20 %) in the AUC of buspirone suggesting there was a small inhibition of CYP3A4 activity caused by green tea catechin. Of interest, the authors estimated the daily administration of 800 mg of EGCG (i.e. four of the capsules) to be equivalent to the EGCG content of 8–16 cups of green tea (Chow et al., 2006). Because no clinically relevant changes in CYP phenotypic indices were observed at the selected dose and dosing condition, potential for drug interactions is unlikely with regular green tea consumption at lower catechin content. The authors concluded that repeated green tea catechin administration is not expected to result in clinically significant effects on the disposition of drugs metabolized by these CYP enzymes. In addition, the discrepancy in the findings on CYP3A4 observed by Chow et al. (2006) and Donovan et al. (2004) might be related to different sample sizes used in these studies. With a sample size of 11 in Donovan et al. (2004) study, it may not be powerful enough to detect small changes in CYP3A4 enzyme activity. The lack of effect on CYP3A4 activity could also be due to disparity in the sensitivity of different probe drugs to enzyme modulations because the same CYP3A4 inhibitors led to greater changes in AUC of buspirone than that of midazolam AUC (Bjornsson et al., 2003; Schönthal, 2011). In our opinion, the inconsistency of findings may also be due to variability in total phenol and catechin contents in green tea products used. It has been shown that there is considerable variability both in total phenol and catechin content (as well as caffeine content), depending on the brand of product, the region the tea was grown, the age of the leaves, the manufacturing process conditions, infusion time, etc. (Astill et al., 2001; Khokhar and Magnusdottir, 2002).

Even though dried green tea leaves have been found to contain substantial amounts of vitamin K, however brewed green tea is normally not regarded as a significant source of the vitamin. However, large amounts of brewed green tea might reduce the anticoagulant effect of warfarin (Heck et al., 2000). A 44-year-old patient with a mechanical heart valve received warfarin therapy. The INR of this patient decreased markedly when he started drinking large amounts of brewed green tea (Taylor and Wilt, 1999). The patient turned up to the outpatient clinic with an INR of 1.37; his INR 22 days prior to this visit had been 3.79. The patient was unable to be reached until his return visit to the clinic one month later, at which time his INR was 1.14. In an interview, the patient disclosed that he had started drinking 0.5-1 gallon of brewed green tea daily about one week before the INR measurement of 1.37. There were no other recognizable causes of the remarkable decrease in the INR, including changes in the patient's medications, dietary intake, medication compliance, or medical conditions. A substantial drop in the INR would not typically be expected to result from regular consumption of moderate amounts of brewed green tea. Generally it is not necessary to advise patients getting warfarin therapy to avoid green tea. Nevertheless, patients should be advised that large quantities of green tea may diminish the effectiveness of warfarin therapy (Heck et al., 2000).

Collectively, a number of studies revealed the lack of effect of regular green tree consumption on the activities of human CYP enzymes including CYP1A2, CYP2C9, CYP2D6, and CYP3A4. Thus it is suggested

that drinking green tree or taking green tree extract as dietary supplements, at regular doses is unlikely to cause adverse drug interactions with prescription drugs which are metabolized by these CYP enzymes. Although a clinical study by Chow et al. (2006) highlighted the 4-week green tea extract mediated interaction with the CYP3A4-metabolized drug, buspirone, the underlined mechanism of this interaction remains to be clarified. The variability between subjects suggested a possible pharmacogenetic predisposition for green tea interactions. While awaiting further information and experiments in humans, consumption of green tea and green tea extract should be monitored in patients receiving drugs metabolized by CYP3A4. Also patients who are prescribed drugs with a narrow therapeutic index such as warfarin should be cautioned about the effects green tea consumption may have on their treatment.

Kava (Piper methysticum)

Kava (*Piper methysticum* G Forst, Family Piperaceae) is a shrubby plant indigenous to the South Pacific Islands, including Hawaii, Vanuatu, Polynesia, Melanesia and some parts of Micronesia. An extract from the rhizome and roots of kava have been used in the South Pacific as part of a recreational and ceremonial drink for 2000 years (Lebot et al., 1997). The commercial products are prepared from dried rhizomes of the kava plant, and the more contemporary dosage form it is a capsule, which usually contain a standard 30 % of kavalactones (Zadoyan and Fuhr, 2012). The constituents of kava extract are kavalactones, kawain, methysticin, dihydromethysticin, desmethoxyyangonin, and dihydrokawain (Shord et al., 2009). In Western countries, dietary supplements containing kava are used for the treatment of anxiety and to relieve stress and tension, as well as for sleeplessness and menopausal symptoms (Teschke, 2010; Teschke and Schulze, 2010). The available evidence suggests that kava extracts are superior to placebo for treating patients with anxiety disorders (Sarris et al., 2011). Kava-containing products remain popular in the United States and continue to be sold in health food stores and ethnic markets. However, it was banned in many Western countries such as UK, Germany, France, Switzerland, Australia, and Canada, following reports of suspected hepatotoxicity (Capasso et al., 2003; Lim et al., 2007).

Although the alteration in CYP enzyme activity is one of the important causes of herbal drug interactions, there were only a few human studies existing to evaluate the clinical relevance of potential CYP-mediated interactions caused by kava. In an early study, single-time point phenotypic metabolic ratios were employed to determine whether long-term supplementation of kava (*Piper methysticum*) extract affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity (Gurley et al., 2005). Twelve healthy subjects were randomly assigned to receive kava for 28 days. Probe drug cocktails of midazolam (CYP3A4) and caffeine (CYP1A2), followed 24 hours later by chlorzoxazone (CYP2E1) and debrisoquine (CYP2D6), were administered before (baseline) and at the end of supplementation. Pre-supplementation and post-supplementation phenotypic trait assessments were determined for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 as described previously (Gurley et al., 2002). Comparisons of pre-supplementation and post-supplementation phenotypic ratios revealed that kava significantly reduced the serum ratio of 6-hydrochlorzoxazone to chlorzoxazone, a measure of CYP2E1 catalytic activity, by 40 %. This indicates that kava supplementation caused a considerable inhibition of human CYP2E1 enzyme activity (Gurley et al., 2005). It may suggest that taking kava concomitantly with drugs that are metabolized by CYP2E1 is likely to cause an herbal drug interaction. On the other hand, kava supplementation had no considerable effect on the activity of other CYP studied, i.e., CYP1A2, CYP2D6, and CYP3A4 (Gurley et al., 2005).

The potential effect of kava on human CYP3A4 activity was investigated by the same group of researchers (Gurley et al., 2008a). In this randomized trial, 16 healthy volunteers were randomly assigned to receive either goldenseal or kava for 14 days. Each supplementation phase was followed by a 30-day washout period. Midazolam was used as a CYP3A4 probe and was orally administered before and after each phase, and pharmacokinetic parameters were determined. The results showed that kava did not alter the pharmacokinetics of midazolam (CYP3A4), indicating that the concomitant ingestion of kava does not inhibit CYP3A4 activity. This supports the earlier study conducted by these investigators (Gurley et al., 2005), finding lack of effect of kava on human CYP3A4 activity. This evidence suggests that herbal drug interactions are unlikely to occur when the patients concomitantly take kava dietary supplements with CYP3A4 substrate drugs.

Regarding CYP2D6 which is an important CYP isoform as it accounts for the metabolism of approximately 30 % of all medications, there were few *in vivo* studies have assessed the effects of kava on CYP2D6 activity. Six herbal extracts including kava were evaluated in three separate studies, each incorporating 16 healthy volunteers (Gurley et al., 2008b). Subjects were randomized to receive a standardized herbal extract (including kava) for 14 days on separate occasions. The CYP2D6 probe, debrisoquine (5 mg), was administered before and at the end of supplementation. Pre- and post-supplementation phenotypic trait measurements were assessed for CYP2D6 using 8-hour debrisoquine urinary recovery ratios. Comparisons of pre- and post-supplementation results revealed no significant inhibition of CYP2D6 after post-supplementation of kava extract. This suggests that kava does not notably change the activity of human CYP2D6. Accordingly, it is doubtful that adverse herbal drug interactions would result with concomitant ingestion of kava supplements and drugs that are metabolized by CYP2D6 (Gurley et al., 2008b).

Of interest, kava may also inhibit human CYP1A2 activity based on evidence obtained from a clinical study (Russmann et al., 2005). These investigators aimed to determine whether clinically relevant interactions were to be anticipated from the consumption of the aqueous extract of kava root (*Piper methysticum*), which is common in the South Pacific. This study was conducted in 6 New Caledonian healthy subjects who consumed traditional aqueous kava extract regularly for more than 6 years. It was estimated that they drank approximately 7-27 g of kavalactones per week up to the beginning of the study. The participants were requested to stop kava consumption for 30 days without any other change in their lifestyle including diet, smoking, and medication and to undergo 2 sessions of CYP phenotyping by using a single time point phenotypic ratio method as described previously (Gurley et al., 2002). Metabolic ratios for 5 different probe drugs including caffeine (CYP1A2), mephenytoin (CYP2C19), debrisoquine (CYP2D6), chlorzoxazone (CYP2E1), and midazolam (CYP3A4) were determined before and after a 30-day complete abstinence from kava. Their results have shown that kava consumption had no significant effect on the activities of CYP2C19, CYP2D6, CYP2E1 and CYP3A4. These results with CYP2C19, CYP2D6 and CYP3A4, are in agreement with previous reports cited by other researchers (Gurley et al., 2005, 2008a, b). However, with respect to CYP2E1 finding, lack of effect by kava on CYP2E1 is in contrast with previous data obtained by Gurley et al. (2005) who reported that kava supplementation caused a considerable inhibition of human CYP2E1 enzyme. Russmann et al. (2005) found interesting results regarding the potential interaction of kava and CYP1A2. The mean caffeine metabolic ratio increased significantly (2-fold), from 0.3 with the consumption of kava to 0.6 at 30 days after cessation of kava. This suggests that traditional kava drinking inhibits human CYP1A2 en-

zyme activity. In view of this inhibitory effect, caution should be used in consumers of kava who are prescribed drugs that are metabolized by CYP1A2 (e.g., theophylline, *R*-warfarin, fluvoxamine, and tizanidine). On the other hand, CYP1A2 is responsible for the metabolic activation of potent carcinogenic environmental toxins such as aflatoxins, and aflatoxin exposure is a problem in the warm and humid climate of the South Pacific. A previous study suggested an inverse correlation between cancer incidence and kava consumption for a number of Pacific Island Nations (Steiner, 2000). Therefore, inhibition of CYP1A2 by kava consumption may be of health benefit because kava consumption could thus provide a protective effect against environmental carcinogens (Russmann et al., 2005).

Overall, even though there were few clinical studies conducted to assess the clinical relevance of potential CYP-mediated interactions caused by kava, existing data indicate that kava supplements have the potential to inhibit a few CYP enzymes. The significant inhibitions caused by kava include CYP1A2 and CYP2E1. Thus, taking kava dietary supplements or drinking traditional aqueous kava extract may result in an interaction with prescription drugs that are metabolized by either CYP1A2 or CYP2E1 enzyme. Caution is advised to be taken when the patients administrate kava with CYP1A2 or CYP2E1 substrate drugs because it may increase their therapeutic and adverse effects.

Saw palmetto (Serenoa repens)

Saw palmetto (*Serenoa repens*, Family-Arecaceae) is used in many forms of traditional herbal medicine. Native American Indians used the fruit for food and to treat a variety of urinary and reproductive system problems. Saw palmetto extract is an extract of the fruit of Serenoa repens and widely used as dietary supplement. It is abundant in fatty acids and phytosterols. It has been used in traditional and alternative medicine to treat a variety of disorders. It was reported that preparations of saw palmetto are well tolerated by most users and are not related with dangerous adverse incidents Saw palmetto extract is the most popular herbal preparations for the treatment of benign prostatic hyperplasia (Tacklind et al., 2002), a common condition in older men. Some people also use saw palmetto for colds and coughs, sore throat, asthma, chronic bronchitis, chronic pelvic pain syndrome, and migraine headache. In addition, saw palmetto is used as a diuretic, to promote relaxation (as a sedative), and to enhance sexual desire (as an aphrodisiac).

Saw palmetto is used concomitantly with prescription medications. A recent study of men taking an herbal product for the treatment of benign prostatic hyperplasia showed that 60 % of them were also taking a prescription medication for benign prostatic hyperplasia (Eisenberg et al., 1998). Up todate, there is no evidence for drug interactions with saw palmetto. Two clinical studies have shown that saw palmetto had no significant effect on a number of CYP enzymes in healthy volunteers. The first study was conducted in healthy volunteers to verify if a preparation of saw palmetto altered the activity of two important drug metabolizing enzymes, CYP2D6 and CYP3A4 (Markowitz et al., 2003). These two enzymes were selected for assessment as, they together contribute to the metabolism of more than 50 % of clinically used prescription and over-the-counter medications (Wrighton and Thummel, 2000; Zanger and Eichelbaum, 2000). The probe substrates dextromethorphan (CYP2D6 activity) and alprazolam (CYP3A4 activity) were administered orally at baseline and again after administration of saw palmetto (320 mg capsule once daily) for 14 days. The mean ratio of dextromethorphan to its metabolite observed at the baseline was not significantly different from that after 14 days of saw palmetto administration. This indicates a lack of effect of saw palmetto co-administration on CYP2D6 activity (Markowitz et al., 2003). There were no significant differences between the elimination half-life and AUC of alprazolam at

baseline and that after saw palmetto treatment. This suggests that saw palmetto co-administration has no effect on CYP3A4 activity. Their results imply that extracts of saw palmetto at generally recommended doses are unlikely to alter the disposition of co-administered medications primarily metabolized by human CYP2D6 or CYP3A4 for elimination (Markowitz et al., 2003). However, these conclusions must be considered in the circumstance of the study's limited assessments and viewed as only the preliminary study into the drug interaction potential of saw palmetto. In the second clinical study (Gurley et al., 2004), single-time point phenotypic metabolic ratios were used to examine whether long-term supplementation of saw palmetto (*Serenoa* repens) extract affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity. The study was carried out in 12 healthy volunteers. They were pretreated with saw palmetto for 28 days. Probe drug cocktails of midazolam and caffeine, followed 24 hours later by chlorzoxazone and debrisoquine, were administered before (baseline) and at the end of supplementation. Pre-supplementation and post-supplementation phenotypic trait measurements were determined for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 by use of 1-hydroxy-midazo-lam/midazolam serum ratios (1-hour sample), paraxanthine/caffeine serum ratios (6-hour sample), 6-hydroxychlorzoxazone/ chlorzoxazone serum ratios (2-hour sample), and debrisoquine urinary recovery ratios (8-hour collection), respectively. Comparisons of pre-supplementation and post-supplementation phenotypic ratios suggested that saw palmetto supplements had no significant effect on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity. The authors concluded that botanical supplements containing saw palmetto extract appear to pose a minimal risk for CYP-mediated herbal drug interactions in humans (Gurley et al., 2004). The presently existing evidence indicates that saw palmetto is not likely to cause serious health threats to patients taking saw palmetto concomitantly with prescription drugs.

Chinese herbal medicines

Chinese herbs are part of traditional Chinese medicine and have been used for thousands of years in China (Leung, 2006). Recently, Chinese herbs have become more popular in the Western world (Youns et al., 2010). Many cancer patients often use Traditional Chinese Medicine (TMC) treatments to improve general health, to strengthen immunity and to reduce side effects of conventional cancer therapies as well as to increase quality of life (Wong et al., 2001; Xu et al., 2006; Youns et al., 2010). The traditional Chinese medicines are also used for treatment of other diseases such as rheumatoid arthritis, obesity and HIV/AIDS (Zhang et al., 2010; Wang and Zou, 2011; Sui et al., 2012). When patients take conventional drugs concomitantly with Chinese herbs, herbal drug interactions can occur and could produce unwanted outcomes. Some pharmacodynamic interactions involved with Chinese herbal medicines have been previously reported. For instance, concomitant administration of warfarin and some particular Chinese herbs including ginseng (ren shen), Ginkgo biloba (yin xing), Salvia miltiorrhiza (danshen), and Angelica sinensis (dong quai) has been found to initiate an increased INR (international normalized ratio). Usually extensive bleeding was observed in these patients as a consequence of the anticoagulation and antiplatelet properties of these herbs (Fugh Berman, 2000; Izzo, 2005). With limitation of our article’s scope, only reported pharmacokinetic interactions caused by these Chinese herbal medicines will be reviewed in detail.

Moreover, Chinese herbs may also lead to pharmacokinetic interactions by modulation of drug metabolizing enzyme activities (Lau et al., 2013; Yu et al., 2011), such as the phase I metabolizing CYP enzyme family. Of this family, CYP3A4 is judged the most important enzyme because it is responsible for the metabolism of most currently used drugs (Pal and Mitra, 2006; Scripture and Figg, 2006). Inhibition of CYP3A4 can lead to increased plasma levels of drugs that

are substrates for CYP3A4 and thus can cause toxicity. In contrast, induction of CYP3A4 can result in decreased plasma drug levels and subsequently diminish drug's efficacy (Lau et al., 2013). Since numerous anticancer, immunosuppressive and antiviral drugs have a narrow therapeutic window, pharmacokinetic interactions between Chinese herbs and conventional medications could have remarkable consequences. Even though Chinese herbs have the potential to cause pharmacokinetic and pharmacodynamic interactions, patients usually believe they are safe to use because they are derived from natural sources (Lau et al., 2013; Youns et al., 2010). Little is also known regarding the risks and effects of interactions between traditional Chinese medicines and conventional medications. These Chinese herbal drug interactions are also often under-testified (Fasinu et al., 2012; Fugh Berman, 2000; Ge et al., 2014). In this review, possible drug interactions with ginseng (ren shen) has been described in this current report, while those with Ginkgo biloba (yin xing) were discussed before in previous review article – Part 1 published in this journal (Wanwimolruk and Prachayasittikul, 2014). Some other important Chinese medicines and possible drug interactions are reviewed as follow.

(i) Danshen (Salvia miltiorrhiza)

Danshen, also recognized as Chinese salvia or red salvia, are herbal preparations derived from the roots and rhizome of *Salvia miltiorrhiza* (Family Lamiaceae). Danshen is commonly used in traditional Chinese medicine for the treatment of numerous conditions including cardiovascular disease, hypertension, and ischemic stroke (Ernst et al., 2008; Hatfield et al., 2013; Izzo, 2012). Danshen can affect haemostasis in several ways, including inhibition of platelet aggregation. Case reports have identified danshen as an agent that caused the overanticoagulation and bleeding complications in patients who were become stable on warfarin therapy and took this herbal preparation concomitantly (Chan 2001; Yu et al., 1997). Studies in rats have shown that danshen can increase the bioavailability of both R- and S-warfarin (Chan et al., 1995), therefore magnifying the anticoagulant response of warfarin. Not surprisingly, patients receiving warfarin therapy may present with overanticoagulation and bleeding complications when they also take danshen (Chan 2001). Because of the risk of these pharmacokinetic and pharmacodynamic interactions, danshen should be avoided in patients taking warfarin.

In recent years, some studies have revealed the effect of danshen extract on CYP3A4. Ethyl acetate extract (lipophilic components) of danshen has shown to be able to induce CYP3A in C57BL/6J mice (Kuo et al., 2006). Yu et al. (2009) have demonstrated that lipophilic components of danshen extract (tanshinone IIA and cryptotanshinone) were good agonists for pregnane X receptor (PXR) involved in the induction of CYP3A4. Treatment of LS174T cells with cryptotanshinone or tanshinone IIA caused a significant increase of CYP3A4 mRNA (Yu et al., 2009). They concluded that activation of PXR and the resultant CYP3A4 induction was facilitated by cryptotanshinone and tanshinone IIA, the active components of danshen. An *in vitro* study using liver microsomes reported that seven (three lipophilic and four hydrophilic) components of danshen extract had no inhibitory effect on CYP3A4 enzyme activity (Qiu et al., 2008). These findings suggested that danshen extract could induce human CYP3A4 enzymes and this can lead to significant drug interaction with CYP3A4 substrate drugs. This was supported by finding from a clinical study conducted in 14 healthy volunteers (Qiu et al., 2010). Long term (14 days) administration of danshen tablets caused a significant decrease in oral bioavailability of midazolam, a preferred *in vivo* CYP3A probe. This may be the cause of the induction of intestinal CYP3A4 by the lipophilic components of danshen extract (Qiu et al., 2010). Of note, if an orally administered drug is a CYP3A4 substrate with a low oral bioavailability because of extensive pre-systemic metabolism

by enteric CYP3A4, then co-administration of danshen tablets may have a substantial effect on systemic exposure. Thus, precautions should be taken when patients are taking danshen tablet concomitantly with CYP3A4 substrate drugs (Qiu et al., 2010). This will depend upon the drug's exposure-response relationship. It may require dosage adjustment of CYP3A4 substrate drugs in patients receiving concomitant therapy with danshen preparations (Qiu et al., 2010). In addition, an extensive review on the effects of danshen and its active ingredients on the interactions of CYP and drug transporters have been published recently (Zhou et al., 2012).

(ii) Dong Quai (Angelica sinensis)

Angelica sinensis (Family Apiaceae), commonly recognized as "dong quai","dong gui" or dang gui (various spellings), is one of the most popular traditional Chinese medicines (Capasso et al., 2003; Hirata et al., 1997; Kan et al., 2008). Preparations from its roots are used mainly for dysmenorrhea and menopausal symptoms (Circosta et al., 2006; Hirata et al., 1997). It is also used for the treatment of anemia, chronic bronchitis, asthma, rheumatism and cardiovascular diseases (Tang et al., 2006). It is recorded that 70 formulae in China and 56 formulae in Japan contain dong quai. Dong quai is commonly used in Asia, and dong quai is also consumed as a health food product for women's care in Europe and America. The actions of dong quai are thought to be due to the presence of a number of chemical constituents, including coumarins, which may have anticoagulant actions (Capasso et al., 2003; Lau et al., 2013). Two case reports were recorded and suggested that the major consequences of warfarin and dong quai interaction were increased bleeding risks due to the additive anticoagulant or antiplatelet effects of dong quai (Ellis and Stephens, 1999; Page and Lawrence, 1999; Tsai et al., 2013). For patients taking conventional anticoagulants such as warfarin concomitantly with dong quai, the potential risks of increased bleeding as a consequence of herbal drug interactions must not be overlooked (Tsai et al., 2013). The effects of dong quai directly on CYP activities were solely investigated in *in vitro* (Lau et al., 2013; Tang et al., 2006). Even though these *in vitro* results showed strong inhibition or induction of dong quai against a number of human CYP enzymes including CYP1A2, CYP2D6, CYP2C9, CYP2E1 and CYP3A4, the consequence of these interactions is necessary to be proved by clinical studies. If the data are extrapolated to humans, these changes might be very critical, especially when this Chinese medicine is used over long periods of time. Under these conditions, the enzymatic induction/inhibition would be long-lasting, and alterations in the pharmacokinetics of concomitant drugs can happen (Guerra et al., 2000). Thus, attention should be given to the possible drug interaction in patients concurrently using dong quai and drugs that are CYP substrates. Lack of clinical studies on drug interactions with this popular Chinese medicine dong quai, suggests future research on this area is crucially warranted.

(iii) Bai Hua She She Cao (Oldenlandia diffusa)

Oldenlandia diffusa (Willd.) Roxb. is a member of the Rubiaceae Family. The plant is known as Hedyotis diffusa (botanical name), Herba hedyotis diffusae (pharmaceutical name) and Bai Hua She She Cao as a common Chinese name. It is a well-known medicinal plant commonly used in Southern China for the treatment of hepatitis, tonsillitis, sore throat, appendicitis, urethral infection, rheumatism, arthritis, autoimmune disease, and malignant tumors of the liver, lung, and stomach (Gupta et al., 2004; Ovesna et al., 2004).

Oldenlandia diffusa was found to slightly inhibited CYP3A4 activity *in vitro* (Lau et al., 2013). However, its potency on inhibition of CYP3A4 was much less than ketoclonazole. Interestingly, Oldenlandia diffusa was reported to cause significant induction of both PXR-mediated CYP3A4 and CYP3A4

mRNA levels (Lau et al., 2013). These results have shown that the strength of the CYP3A4 induction mediated by Oldenlandia diffusa was as strong as caused by rifampicin and St. John's wort, two very potent CYP3A4-inducers and well-known in clinical setting (Lau et al., 2013). Coadministration of rifampicin or St. John's wort with a CYP3A4 substrate drug was known to decrease plasma levels of CYP3A4 drugs, such as the anticancer drug imatinib, the immunosuppressant cyclosporine and the antiviral drug indinavir (Borrelli and Izzo, 2009; Niemi et al., 2003). Thus, herbal drug interactions caused by taking Oldenlandia diffusa concomitantly with these CYP3A4 drugs are highly possible. As this Chinese herb Oldenlandia diffusa is commonly used for treatment of various illnesses including cancers (Gupta et al., 2004; Ovesna et al., 2004), potential Chinese herbal drug interactions need to be evaluated *in vivo*. This may be very feasible in cancer patients already consuming Chinese herbs in conjunction with their chemotherapy. These patients could be suitable candidates to evaluate pharmacokinetic interactions between Chinese herbs and anticancer drugs.

(iv) Dang shen (Codonopsis tangshen)

Dang shen or Chuan-Denshen is the root of *Codonopsis tangshen, Oliv*. (Family Campanulaceae). It is a well-known traditional Chinese medicine, sometimes used as a cheap substitute for ginseng. This Chinese medicine has been used as a traditional remedy for replenishing energy deficiency, strengthening the immunological system, lowering blood pressure and improving appetite (Fu et al., 1999; Juangsu New Medical College, 1979). Codonopsis tangshen roots have also been demonstrated to possess other pharmacological effects such as antiulcer activities, antiplatelet activities and anticancer activities (Fu et al., 1999). Despite the wide use of this Chinese herbal medicine, there is very little information on drug interactions with Codonopsis tangshen. To our knowledge, there was only one *in vitro* study that investigated the possible interactions of selected Chinese herbs including Codonopsis tangshen on human CYP3A4 enzyme (Lau et al., 2013). As compared with other Chinese medicines (Oldenlandia diffusa and Rehmannia glutinosa), Lau and co-workers (Lau et al., 2013) found that Codonopsis tangshen hardly induced CYP3A4. In addition, Codonopsis tangshen slightly inhibited CYP3A4 enzyme activity. However, its inhibitory effect was observed to be much less than that of other two Chinese medicines, i.e., Oldenlandia diffusa and Rehmannia glutinosa (Lau et al., 2013). These results may imply that drug interactions with Codonopsis tangshen are unlikely, at least with regarding to the important human drug metabolizing enzyme CYP3A4. Nevertheless, clinical studies are required to confirm the lack of drug interactions with this particular herbal medicine.

(v) Sheng di huang (Rehmannia glutinosa)

Rehmannia glutinosa is one of the fifty principal herbs used in traditional Chinese medicine, where it has the name “Sheng Di Huang” in Chinese, and known as Sook-Ji-Whang or To-Byun in Korea. A steamed root of Rehmannia glutinosa has been used for regulation of immune response and shown to improve memory (Cui et al., 2003). It has also been reported that Rehmannia glutinosa possesses anti-allergy effects and anti-inflammatory functions (Kim et al., 1998, 1999; Sung et al., 2011; Wu et al., 2011). Only a few *in vitro* studies have been conducted to determine the effects of Rehmannia glutinosa on activity of human CYP enzymes. Yu and co-workers (Yu et al., 2011) have shown that ethanol extracts of 22 traditional Chinese medicines including Rehmannia glutinosa could activate PXR signalling pathway and induce CYP3A4 reporter gene. Thus, it has been suggested that caution should be taken when Rehmannia glutinosa and other Chinese herbal medicines are used in combination with prescribed drugs metabolized by CYP3A4 (Yu et al., 2011). On the other hand, the finding from another *in vitro*

study gave contradictory results. This study was carried to evaluate the potential for herbal drug interactions of CP-001, a standardized herbal mixture of Houttuynia cordata, Rehmannia glutinosa, Betula platyphylla, and Rubus coreanus (Yoo et al., 2013). Rehmannia glutinosa is one of the components in this CP-001 herbal mixture. The study was tested by using *in vitro* human liver microsomal technique. The effects of CP-001 on activities of various CYP isozymes (i.e., CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) were found to be negligible. Thus, the likelihood of drug interactions caused by this herbal mixture is considered minimal. The findings may be extrapolated and applied to Rehmannia glutinosa when it is given as a single herbal medicine. Normally, this would expect that the concomitant use of Rehmannia glutinosa with prescription drugs, is unlikely to cause any significant drug interactions. As no clinical studies have been conducted to confirm this, the findings from *in vitro* investigations may not always be valid. To clarify the clinical relevance of the proposed drug interactions with the popular Chinese herbal medicine Rehmannia glutinosa, further studies are required.

Quality of herbal medicines as a problematic issue

Of note, as most described drug interactions with Chinese herbs were derived from *in vitro* investigations, these must be extrapolated to clinical settings with precaution. For example, the interactions between Chinese medicines and CYP3A4 will only have clinical relevance, if the minimal concentration of herbal ingredients needed to cause these interactions is achieved *in vivo* (Lau et al., 2013). This is dependent upon the physicochemical and pharmacokinetic properties of those herbal active ingredients, such as their lipid solubility, oral bioavailability, absorption, distribution and elimination. Moreover, some other factors such as variation between batches of Chinese medicine products and methods of herbal preparations can further complicate the impact of Chinese herbal drug interactions. Quality control is a major problem associated with herbal medicines because the manufacture of herbal medicines is not subject to the same regulations as prescription drugs (Wanwimolruk and Prachayasittikul, 2014). Thus, the content of the active ingredients may vary among manufacturers or product batches, possibly causing a large variation in efficacy and safety. Different batches of Chinese herbs can have different compositions of ingredients, including the active compounds which are able to modulate activity of CYP3A4 enzyme (Lau et al., 2013). Therefore, various batches can have different consequences on herbal drug interactions. As reported for Rehmannia glutinosa (Zhang et al., 2008), the processing of raw herbs can lead to differences in herbal compositions among the batches. These differences in herbal active composition will impact the overall outcome of herbal drug interactions. It may produce contrasting results in herbal drug interactions when compared to the results derived from different studies. Products from different manufacturers of the same herb may have different active herbal compositions and hence different biological effects are produced. Also these may cause different outcomes of herbal drug interactions such as one may produce significant drug interactions whereas the other causes no significant interactions. The problem of lack of quality control of herbal products causing variation in their active ingredients is a main concern for every herbal product, not only for Chinese medicines. This has been recognized with three well-known herbal supplements including St. John's wort, ginseng and ephedra. The contents of active ingredients in these herbal supplements were reported to vary widely between brands and in some cases the content variation was also found between batches of the same herbal products (Draves and Walker 2003; Gurley et al., 2000; Harkey et al., 2001). Therefore, it has been proposed that the same rigorous regulations that apply to conventional drugs with

respect to quality, safety and efficacy should be demanded for herbal medicines.

CONCLUSION

Herbal medicines have been commonly used over thousands of years, and they have gained popularity over the last decades. Now it is well recognized that herbal drug interactions are real and have potential to occur when patients take herbal medicines concomitantly with conventional drugs. The most important example of herbal drug interactions is the interactions with St. John's wort as these interactions have caused significant clinical outcomes. Details of the St. John's wort drug interactions are described in previous review articles (Hu et al., 2005; Izzo and Ernst, 2009; Johne and Roots, 2005; Shi and Klotz, 2012; Wanwimolruk and Prachayasittikul, 2014). Many studies have been focused on trying to identify potential herbal drug interactions. Unfortunately, most of these investigations were carried out either in animals or *in vitro*. It is common that there were discrepancies between results of animal or *in vitro* studies and those derived from human studies. Therefore, caution must be exercised both in the absence of human studies and with respect to reliance on lab-based evidence (Shi and Klotz, 2012). With existing evidence in humans, the herbs described in this review, only kava and green tea have shown significant potential for herbal drug interactions, especially when they are taken with narrow therapeutic drugs. In contrast, other well-studied herbs including black cohosh, ginseng, grape seed extract and saw palmetto appeared to present no drug interactions or cause a minor interactions with drugs that are metabolized by human CYP enzymes. With respect to Chinese herbal medicines, although they are widely used among Asian people, their potential interactions with conventional medicines may be under reported. Importantly, there is lack of evidence in humans to verify if the potential drug interactions with Chinese herbal medicines exist and have clinical consequence. Many existing data on drug interactions with Chinese medicines are derived from either *in vitro* or animal studies. Therefore, this urges us to pay attention to conduct clinical studies which will help to prove clinical relevance of the drug interactions with Chinese medicines.

In summary, herbal drug interactions between herbs and conventional medicines can occur. These are often mediated through modifications of the important human CYP enzymes as most clinically used drugs are substrates of CYP. Evidence has been demonstrated clearly that herbal drug interactions can be of clinical relevance. Therefore, caution should be taken when patients take herbal medicines or herbal supplements together with conventional medicines. Consultation with patients regarding the use of herbal medicines is essential. Currently, the awareness of herbal drug interactions is improving as we have more information disseminated and academic courses including this topic are taught in schools of medicines and allied health. Despite this, efforts dedicated to prevent herbal drug interactions needs to continue. Further research to investigate the clinical relevance of the interactions caused by herbs and herbal medicines in particular Chinese traditional medicines and other Asian (e.g. Indian, Thai) herbal medicines, is required.

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