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The role of dietary supplements in cytochrome P450-mediated drug interactions

[El papel de los suplementos dietarios en las interacciones de fármacos mediadas por el citocromo P450]

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Abstract

Due in part to the increased consumption of herbal products on a global scale, a sharp rise in the reported number of both *in vitro* and *in vivo* interactions of herbals with prescription drugs that are metabolized by cytochrome P450 (CYP) enzymes has been observed. Popular products such as ginseng, saw palmetto and St. John's wort have demonstrated potent *in vitro* inhibition or induction of CYP activity. While reports of *in vivo* interactions are not as numerous, natural products such as garlic, goldenseal and grapefruit juice have shown the potential to affect CYP activity *in vivo*. As the wide-spread use of herbal and alternative medicines continues, an increased awareness on the part of the research and medical communities should afford safer use of these products in the future.

Keywords: Herbal remedies, Alternative and comparative medicines, Cytochrome P450, Herb-drug interactions, Drug-drug interactions.

Resumen

Debido, en parte, al consumo elevado de productos herbales a escala global se ha observado un incremento en el número de publicaciones relacionadas con las interacciones tanto *in vitro* como *in vivo* de hierbas con fármacos prescritos que son metabolizados por enzimas del citocromo P450 (CYP). Productos populares tales como ginseng, palma serrucho y hierba de San Juan han demostrado una potente actividad *in vitro* de inducción o inhibición de CYP. Los estudios sobre interacciones *in vivo* no son tan numerosos; sin embargo, productos naturales tales como ajo, sello de oro y jugo de toronja afectan la actividad *in vivo* de CYP. Como continúa el amplio espectro en el uso de medicinas herbales y alternativas, es necesario incrementar el conocimiento por parte de los investigadores y las comunidades médicas para garantizar en el futuro el uso más seguro de estos productos.

Palabras clave: Remedios herbales, Medicinas alternativas y comparativas, Citocromo P450, Interacciones fármaco-hierba, Interacciones fármaco-fármaco.

Abbreviations: ADR, adverse drug reactions; DDI, drug-drug interaction; CYP, cytochrome P450; MI, metabolic-intermediate complex.

INTRODUCTION

The use of complimentary and alternative medicines has become an increasingly common trend both in the United States and around the world. The total estimated sales of herbal remedies in the United States alone rose from approximately $2.02 billion in 1994 to over $4.4 billion in 2005 (Ferrier et al., 2006). These sales figures include both herbal monotherapies and the increasingly popular combination therapies. Along with the increase in sales, a concurrent increase in the number of reported adverse safety events relating to herbal supplements has also been reported. A report from 2005 links over 5000 adverse reactions, 17 000 health care visits and 12 000 medical outcomes to the use of dietary supplements (Hurley, 2007).

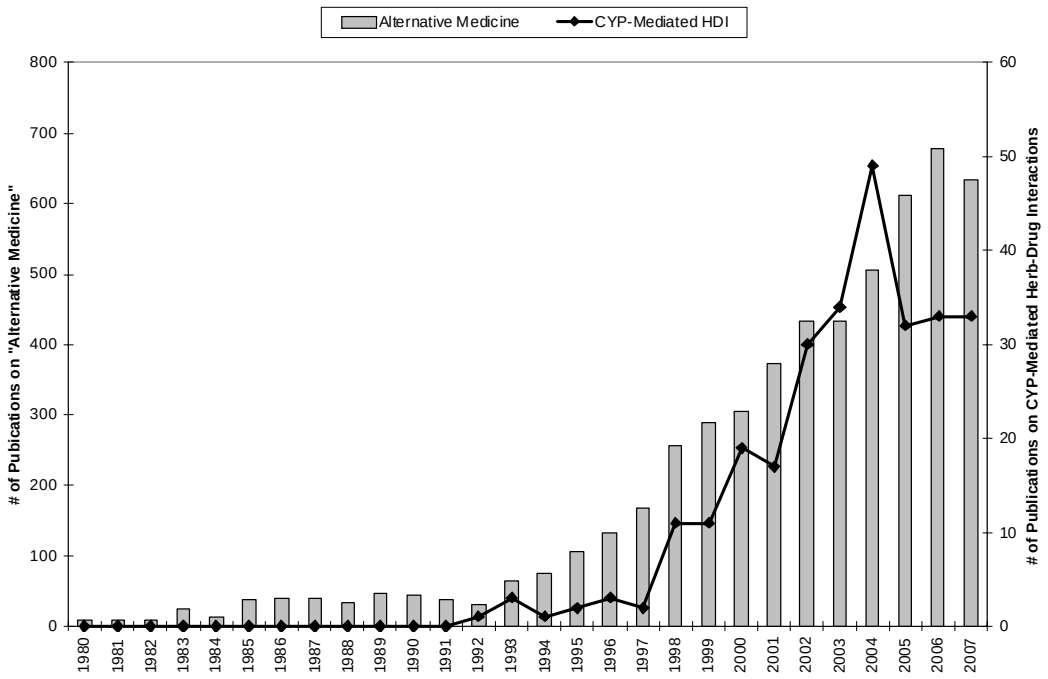
Not surprisingly, the scientific community has also displayed an increased awareness of both the use of alternative medicines as well as there possible role in adverse reactions and drug interactions. A search

of the literature from 1980 through 2007 (SciFinder®) reveals a sharp rise in the number of research articles relating to both the use of alternative medicines as well as to the role of herbal therapies in cytochrome P450-meditated drug interactions (Fig. 1). While manuscripts pertaining to alternative medicines were scarce prior to 1980, there were over 600 such articles published in 2007. In a similar fashion, the number of articles dealing with herbal remedies and drug interactions has increased to approximately 30-40 per year since 2002.

The cytochromes P450 (CYP) are a superfamily of heme-containing enzymes that are involved in the metabolism of the majority of drugs on the market today. The major CYP enzymes that play a role in drug metabolism include CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (Nelson, 2008). Other isoforms, such as CYP2A6, CYP2B6, CYP2C8 and CYP2E1 have also been shown to have important roles in drug metabolism. With adverse drug reactions (ADRs) totaling over 2 million per year in the United States alone (Gurwitz et al., 2000), the ability to predict drug interactions involving the CYP enzymes has become a key component of the drug discovery process.

CYP inhibition can occur in a number of ways, which ultimately can be divided into reversible or irreversible inhibition of the enzyme. Screening for reversible inhibition whereby a perpetrator molecule affects the catalytic capacity of the enzyme towards a second molecule has become commonplace in pharmaceutical research (Rodrigues and Lin, 2001). While the same rigor is not required for herbal-based remedies, a number of very thorough reviews have examined the potential for these substances to interact with CYP enzymes (Ioannides, 2002; Brazier and Levine, 2003; Zhou et al., 2003; Delgoda and Westlake, 2004; Zhou et al., 2004a; Zhou et al., 2004b; Izzo, 2005). The potential for herbal remedies to induce CYP levels has also been examined (Raucy, 2003; Tirona and Bailey, 2006). While this review will deal primarily with inhibition of CYP activity, herbals such as St. John's wort (CYP1A2, CYP2C9, CYP2C19, CYP2E1 and CYP3A4), *Echinacea* (CYP3A4) ginkgo (CYP2C19) and ginseng (CYP2C9) have been shown to be CYP inducers as well (Tirona and Bailey, 2006).

Figure 1. The number of publications by year (1980–2007) pertaining to alternative medicine (vertical bars; left y-axis) or CYP-mediated herb-drug interactions (HDI, solid line; right y-axis).



Metabolic bioactivation of a compound may also lead to CYP-mediated drug interactions (DDIs). The general terminology for loss of CYP activity over time due to compound turnover is time-dependent inhibition. The time-dependence may be due to formation of an inhibitory metabolite, formation of a covalent linkage to the apoprotein, or formation of a linkage to or destruction of the prosthetic heme. If a number of additional criteria are met, such as a 1:1 stoichiometric ratio of inactivator to enzyme and a lack of enzyme activity restoration after dialysis, the compound may be referred to a mechanism based inactivator. The *in vitro* potency of a time dependent inhibitor is defined by two terms, K_I and k_{inact}. The K_I parameter indicates the inhibitor concentration necessary to produce a half-maximal rate of inactivation, while the k_{inact} parameter reflects the maximal inactivation rate. Intermediates formed by CYP-mediated metabolism may also escape the CYP active site and react with other cellular constituents such as proteins or DNA (Uetrecht, 2003), although the potential resultant toxicity may be unrelated to DDIs. A number of natural products with varying structural motifs known to be time-dependent CYP inhibitors *in vitro* are shown in Fig. 2.

It is important to note that while numerous examples of herbal remedies that inhibit CYP activity *in vitro* have been reported, many of these drug interactions do not translate into the clinic. A number of experimental explanations for this disconnect have been proposed, including extraction techniques and solvents used *in vitro* and the poor absorbance/bioavailability properties of the marketed products *in vivo* (Gurley, 2005). In fact, one of the biggest criticisms given to *in vitro* screening of herbal-drug interactions is the lack of clinical evidence to support the *in vitro* findings. Fortunately, as alternative therapies become more popular, the number of clinical drug interaction studies with these remedies has also increased.

The focus of this review will be to examine the potential of commonly used herbal remedies to interact with CYP-mediated drug metabolism. With research constantly ongoing, the number of CYP-mediated herb-drug interactions is also constantly increasing. A comprehensive list of herbal remedies known to be CYP inhibitors *in vitro* is shown in Table 1. As our knowledge of herb-drug interactions increases, the ability to monitor and predict negative outcomes when alternative therapies are co-prescribed with conventional medicines should also increase.

Herbal Remedies that Interact with Cytochrome P450-Mediated Drug Metabolism

Angelica dahurica

The *Angelica dahurica* root, more commonly known as *Bai Zhi*, has been used in traditional Chinese medicine for thousands of years. Uses of the root are numerous, though it has been shown to have analgesic, antibacterial, diuretic and stimulating properties. (Duke and Ayensu, 1985; Yeung, 1985). The root has also been shown to be effective in treating certain types of staphylococcus infections (Lechner et al., 2004) and is contraindicated in pregnant women (Chevallier, 1996).

More recently, the *Angelica dahurica* root has been implicated as a potential inhibitor of CYP3A4 *in vitro*. It has been suggested that the inhibitory potential of the root is contained in the numerous furanocoumarin derivatives, which have been isolated from this root (Hata et al., 1963; Hata et al., 1981; Bergendorff et al., 1997; Kimura and Okuda, 1997; Kwon et al., 1997; Guo et al., 2001). Furthermore, inhibition of 6β-hydroxytestosterone formation in liver microsomes was observed when extracts of the root were included in the incubation (Guo et al., 2001).

Black Cohosh

Black cohosh (*Cimicifuga racemosa)* is a perennial plant that is indigenous to North America. The extract from this plant has been used in the treatment of multiple menopause-related disorders, including sleep disturbances, depression and hot flashes (Liske et al., 2002). Though the pharmacological properties of black cohosh have been attributed to its estrogen-like properties, this claim has been widely debated (Mahady et al., 2002; Beck et al., 2003; Dugoua et al., 2006). In addition, the use of black cohosh during pregnancy has been contra-indicated due its potential labor-inducing effects (Dugoua et al., 2006).

In vitro, black cohosh extracts have been shown to be relatively weak inhibitors of CYP activity. The inhibitory activity has been attributed to six triterpene glycosides that were isolated from black cohosh, with CYP3A4 (nifedipine oxidation) IC_{50} values ranging from 0.10 to 7.78 mM (Tsukamoto et al., 2005a). Interestingly, the authors report an IC_{50} value for the whole extract against CYP3A4-catalyzed nifedipine oxidation to be 0.027 mg/ml, a relatively low value when the C_{50} values of the individual components

Table 1. Herbal remedies that are inhibitors of cytochrome P450 activity *in vitro.*

CYP	Herbal Remedies
CYP1A2	Black/green tea, dan shen, devil's claw, Echinacea, fo-ti, ginkgo, ginseng, grapefruit juice, kava, licorice, resveratrol, St. John's wort, wu-chu-yu tang
CYP2B6	Licorice, luteolin
CYP2C8	Devil's claw, fo-ti, ginkgo, usnic acid
CYP2C9	Cranberry, devil's claw, Echinacea, eucalyptus oil, evening primrose, fo-ti, garlic, genistein, ginger, ginkgo, ginseng, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, licorice, luteolin, milk thistle, saw palmetto, St. John's wort, soy, tumeric, usnic acid, valerian
CYP2C19	Devil's claw, Echinacea, eucalyptus oil, evening primrose, fo-ti, garlic, ginko, ginseng, kava, milk thistle, St. John's wort, usnic acid, valerian
CYP2D6	Black cohosh, black pepper, *C. roseus*, devil's caw, dong quai, Echinacea, eucalyptus oil, evening primrose, fo-ti, genistein, ginger, ginseng, ginkgo, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, luteolin, milk thistle, saw palmetto, St. John's wort, soy, yohimbine
CYP2E1	Echinacea, garlic, ginseng, kava, resveratrol, St. John's wort, watercress
CYP3A4	*A. dahurica*, β-carotene, black cohosh, black pepper, black mulberry, black raspberry, *C. aurantium*, cat's claw, chamomile, cranberry, dan shen, devil's claw, dong quai, Echinacea, eluthero, eucalyptus oil, evening primrose, feverfew, fo-ti, garlic, genistein, ginkgo, ginseng, goldenseal, grapefruit juice, grapeseed extract, green tea, kava, licorice, luteolin, milk thistle, oregano, pomegranate, pomelo, red clover, resveratrol, sage, saw palmetto, schisandra fruit, St. John's wort, soy, tumeric, valerian, wild grape

are taken into consideration.

The drug interaction potential of black cohosh has also been evaluated *in vivo* by Gurley, et al. (Gurley et al., 2005b; Gurley et al., 2006a; Gurley et al., 2006b). No effect was observed on CYP3A4 in clinical trials, while only a minor effect was seen for CYP2D6. As such, the potential for clinically relevant drug interactions with black cohosh appears to be low (van den Bout-van den Beukel et al., 2006).

Black Pepper

The use of black pepper (*Piper nigrum)* is often found in traditional anti-diarrheal remedies. The major component that contributes to the pharmacological activity of black pepper is the alkaloid piperine (Hu et al., 2005). In pre-clinical animal models, black pepper has been shown to slow the gastric emptying of both liquids and solids in a time- and dose-dependent fashion (Bajad et al., 2001).

Only limited *in vitro* data on the drug interaction potential of black pepper is available. The interaction of black pepper and CYP3A4-catalyzed verapamil metabolism (to norverapamil and metabolite D-617) in human liver microsomes has been investigated (Bhardwaj et al., 2002). Piperine appeared to be a linear-mixed type inhibitor of CYP3A4 with a K_i of approximately 60 μM for norverapamil and 43 μM for the D-617 metabolite of verapamil. Piperine is also an inhibitor of CYP3A4 in recombinant preparations (Tsukamoto et al., 2002). In addition, multiple alkylamides that were isolated from black pepper showed considerable time dependent inhibition of CYP2D6 activity *in vitro* (Subehan et al., 2006). The most potent time-dependent alkylamides tested also had methylenedioxyphenyl moieties, a structural feature that is known to cause time-dependent inhibition of CYP activity.

Interestingly, there appears to be more data available on the potential of black pepper to cause drug interactions *in vivo*. The interactions of black pepper with propranolol, rifampicin (P-gp interaction), spartein, theophylline and phenytoin have been assessed in clinical trials. In trials with propranolol, an increase in the C_{max} and AUC of a 40 mg dose of propranolol was observed following 20 mg of piperine for 7 days (Bano et al., 1991), possibly indicating that piperine is inhibiting CYP1A1, CYP1A2 and/or CYP2D6 in humans as these are the primary enzymes responsible for the clearance of propranolol (Hu et al., 2005). Similarly, plasma concentrations of spartein, another CYP2D6 substrate, were increased following administration of piperine in human volunteers (Atal et al., 1981). Most likely due to its inhibition of

CYP1A1 and CYP1A2, the AUC and Cmax values following a 150 mg dose of theophylline also increased in clinical trials following 20 mg/day of piperine for 1 week (Bano et al., 1991). Thus it appears that black pepper may affect CYP1A, CYP2D6 and possible CYP3A4 *in vivo*.

β-Carotene

β-carotene is a form of vitamin A that can be found in carrots, sweet potatoes, various greens as well as in dietary supplements (Pitchford, 2003). It is converted to retinal, another form of vitamin A, by β-carotene dioxygenase in the mucosa of the small intestine. As an herbal supplement, claims have been made as to its ability to prevent cognitive decline and age-related macular degeneration, as well as to treat cases of melasma (Kar, 2002; Grodstein et al., 2007; Jones and Smith, 2007). Unfortunately, numerous studies have also reported a link between β-carotene consumption and an increased risk of lung cancer (Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996a; Omenn et al., 1996b).

Limited data on the potential of β-carotene to cause drug interactions is available; however studies have demonstrated that the retinoid may be able to induce CYP3A4 *in vitro*. (Wang et al., 2006). Additionally, others have shown that β-carotene is able to activate human PXR and subsequently induce target genes (such as CYP3A4) that are controlled by PXR (Ruhl et al., 2004).

Catharanthus roseus

The *Catharanthus roseus*, also referred to as *Vinca rosea, Ammocallis rosea* or *Lochnera rosea*, is widely cultivated in tropical and subtropical areas of the world. Traditionally, the plant has been used to treat Hodgkin's disease, diabetes and malaria (Usia et al., 2005; Yaniv and Bachrach, 2005). Some of the plants pharmacological properties may stem from the alkaloids that have been isolated from *Catharanthus roseus*, namely vinblastine and vincristine. The isolated alkaloids are prescribed in chemotherapy regimens, under the brand names Velbe® and Oncovin®, respectively.

In vitro, the extract of *Catharanthus roseus* has been shown to inhibit CYP2D6 activity with an IC_{50} value of 11 μg/mL (Usia et al., 2006). Ajmalicine and serpentine, two additional alkaloids that were extracted from the plant, inhibited the dealkylation of ^{14}C-dextromethorphan by CYP2D6 *in vitro* with IC_{50} values of 0.0023 and 3.51 μM, respectively. In addition, serpentine was shown to be a time-dependent inhibitor of CYP2D6 *in vitro*, with a K_I of 0.148 μM and a K_{inact} of 0.090 min^{-1} (Usia et al., 2005).

Devil's Claw

The herbal remedy devil's claw (*Harpagophytum procumbens)* has gained increasing popularity as an analgesic and a treatment for rheumatic diseases (Gunther and Schmidt, 2005). In a study designed to evaluate the efficacy of devil's claw in treating lower back pain, no significant differences were noted in a group of 44 patients who received an extract of devil's claw when compared to another group of 44 who received rofecoxib (Chrubasik et al., 2003). The active ingredients in devil's claw are believed to be harpagosides, a glycoside derivative, which are found in the root system of the plant.

In an *in vitro* study, extracts from devil's claw were found to primarily inhibit CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (IC_{50} 121 to 335 μg/mL) and CYP1A2 and CYP2D6 to a much lesser extent (IC_{50} ~ 1 mg/mL) (Unger and Frank, 2004).

Echinacea

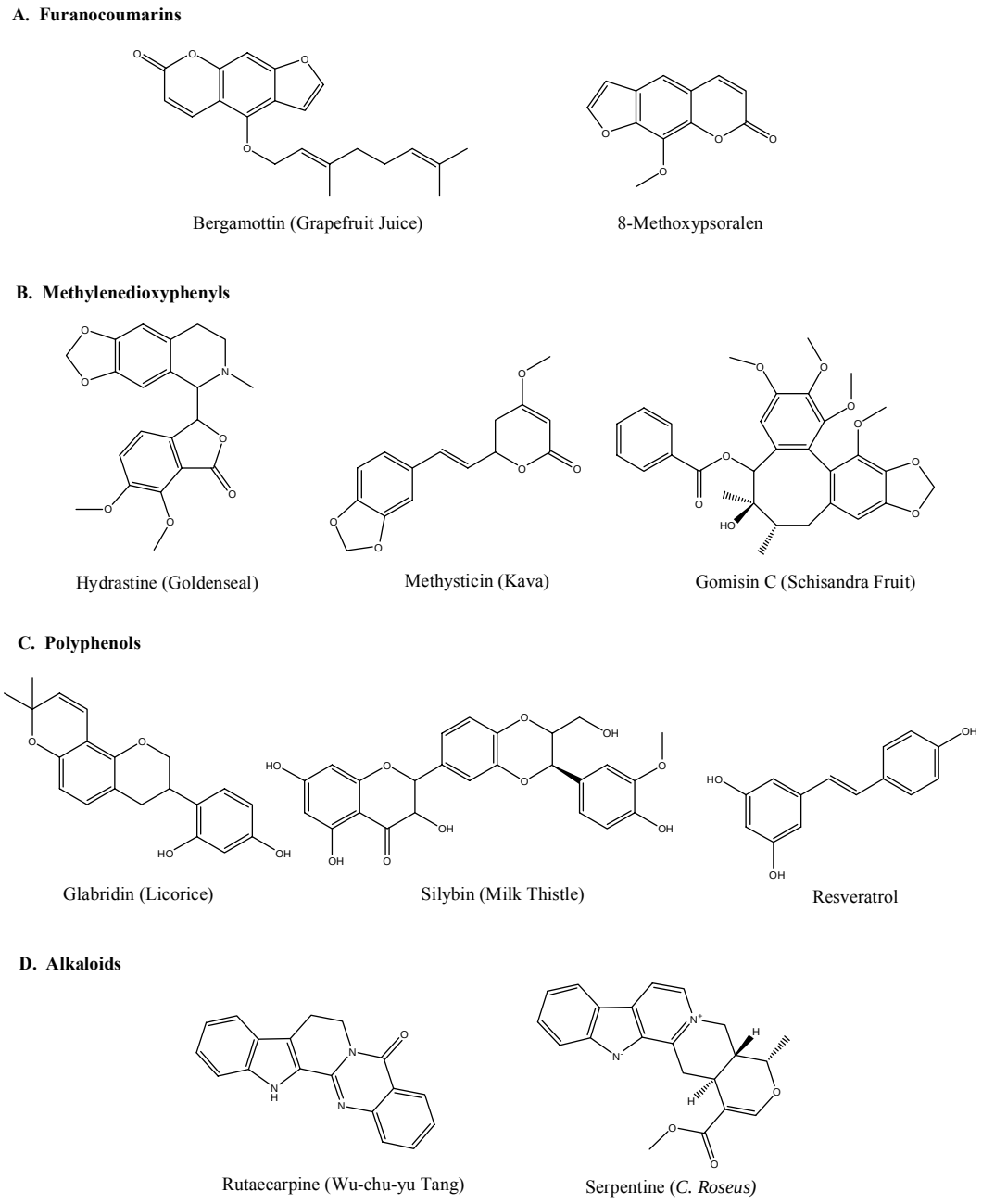
Echinacea (*Echinacea purpurea)* is one of the top selling herbal remedies in the United States. Its most common uses are for the treatment of common cold and influenza symptoms. The immunomodulatory activity of Echinacea is thought to be due the alkylamides that have been isolated from the herb (Woelkart and Bauer, 2007).

Oddly, as popular as Echinacea has become, data surrounding its potential for drug interactions has not been as forthcoming. A recent study in baculovirus-expressed CYP enzymes demonstrated that an Echinacea extract was able to mildly inhibit CYP1A2, CYP2C19, CYP2D6 and CYP3A4 activity (Modarai et al., 2007). Other studies have shown inhibition of CYP2C9 and CYP3A4 activity with no inhibition of CYP2D6 (Yale and Glurich, 2005; van den Bout-van den Beukel et al., 2006). Alkylamides from Echinacea have also been implicated in the inhibition of CYP2E1 at concentrations as low as 25 μM (Raner et al., 2007).

In vivo, the risks of Echinacea induced drug interactions appear to be minor, though further investigation is ongoing. When co-administered to healthy volunteers, the effects of Echinacea extract on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 tend to be relatively small (Gorski et al., 2004; Gurley et al., 2004). In the study by Gorski et al., an induction of

hepatic CYP3A4 activity (approximately 34% increase) was observed, while an inhibition of intestinal CYP3A4 activity was also noted. The two studies also note a possibility of a reduction in CYP1A2 activity *in vivo* due to Echinacea administration. CYP2C9, on the other hand, does appear to be susceptible to inhibition by Echinacea *in vivo*, where a significant increase in the AUC of tolbutamide was observed in the presence of Echinacea (Gorski et al., 2004).

Figure 2. Structures of natural products known to be time-dependent inhibitors of CYP activity *in vitro*. Common structural motifs include furanocoumarin, methylenedioxyphenyl, polyphenol and alkaloid compounds.



Fo-Ti

Multiple herbal therapies that are sold today claim to have estrogen-like properties, including soy, licorice and red clover extracts. Fo-Ti (*Polygonum multiflorum)* is a plant native to China that was shown to contain considerable amounts of estrogen bioactivity (Oerter Klein et al., 2003), which may indicate a potential for the herb to treat symptoms related to menopause. Other therapeutic claims include increased vitality, decreased cholesterol, and relief from constipation.

At higher concentrations *in vitro*, the Fo-Ti root was shown to be an inhibitor of multiple CYP isoforms (Unger and Frank, 2004). Relatively weak inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 was observed with IC_{50} values around 500 µg/mL for all isoforms tested.

Garlic

Numerous reports in the literature support the use of garlic as a therapeutic agent. It has been suggested that garlic may contain antilipidemic, antihypertensive, antiglycemic and antithrombotic properties (Ackermann et al., 2001). It has also been noted that the therapeutic properties of garlic are highly dependent on the preparation and extraction processes used (Greenblatt et al., 2006a).

In vitro, it appears that garlic has the ability to inhibit a number of CYP isoforms, including CYP2C9, CYP2C19 and CYP3A (Foster et al., 2001). Additionally, the diallyl sulfide component found in most garlic preparations has been shown to be an inhibitor of CYP2E1 (Taubert et al., 2006). Conversely, an *in vitro* study that examined the inhibition potential of water soluble components of garlic such as alliin or methylin found no significant inhibition of CYP activity. S-methyl-L-cysteine and S-allyl-L-cysteine showed only a modest inhibition of CYP3A4 *in vitro* (Greenblatt et al., 2006a). Certain components of garlic may also have the ability to increase CYP3A4 activity, though data is somewhat scarce (Wu et al., 2002; Lee et al., 2006b).

Clinical trials using garlic have been limited, though a few studies have reported the inhibition of CYP activity *in vivo*. For instance, following consumption of garlic for 28 days, the *in vivo* activity of CYP2E1 was decreased by approximately 22%. Other studies have noted that no significant effects on CYP2D6 or CYP3A4 activity *in vivo* are likely following consumption of garlic supplements (Markowitz et al., 2003a).

Ginkgo biloba

Ginkgo biloba is often used for its antioxidant and neuroprotective effects. It is claimed that ginkgo can increase circulation and reduce memory loss, cerebral insufficiencies and anxiety or stress levels (De Smet, 2002). Due to its potent anti-platelet properties, the use of ginkgo with other anti-platelet agents such as warfarin or aspirin has been the focus of much debate. Similar pharmacodynamic interactions can also occur if gingko is taken in combination with other herbal remedies that have similar anti-platelet properties such as garlic or ginseng (Sierpina et al., 2003).

Recent data has also demonstrated ginkgo to be susceptible to potential drug interactions *in vitro*. CYP1A1, CYP1A2 and CYP1B1 are all inhibited by *Ginkgo biloba* extracts as indicated by a reduced level of 7-ethoxyresorufin O-dealkylation (Chang et al., 2006). In human liver microsomes, ginkgo was shown to be an inhibitor of CYP2C8 activity (Etheridge et al., 2007). It was also shown to be an inhibitor of CYP2C9 *in vitro*, with a K_i of 14.8 µg/mL (Mohutsky et al., 2006). Ginkgo has the ability to inhibit CYP3A4 *in vitro* (He and Edeki, 2004), though conflicting evidence is available as to whether or not it is an inhibitor of CYP2C19 and CYP2D6 (Zhao et al., 2002; Hu et al., 2005; He et al., 2006; Hellum and Nilsen, 2007).

Multiple *in vivo* studies have also assessed the drug interaction potential of gingko. An *in vivo* study aimed at assessing the effects of ginkgo on CYP2C9-mediated flurbiprofen clearance *in vivo* showed no inhibition of CYP2C9 activity (Greenblatt et al., 2006b). A second study that used (S)-warfarin as a probe of CYP2C9 activity *in vivo* also demonstrated no significant effects due to co-administration with ginkgo (Mohutsky et al., 2006), potentially implying that the CYP2C9 inhibition may only occur *in vitro*. Studies with CYP3A4 and diltiazem, however, showed that gingko increased the AUC and absolute oral bioavailability of diltiazem following a 20 mg/kg dose of ginkgo (Ohnishi et al., 2003; Hu et al., 2005; van den Bout-van den Beukel et al., 2006).

Ginseng

Ginseng is one of the most widely used herbal remedies in the United States and is indicated to provide an enhanced immune system and level of physical stamina as well as to decrease fatigue. Multiple ginseng derivatives are available, with two of the more popular being *Panax ginseng* and Siberian ginseng. The latter is also used as an anti-

inflammatory and anti-cancer agent, and few if any drug interactions have been reported (van den Bout-van den Beukel et al., 2006). In general, a greater focus seems to have been placed on *Panax* or Asian ginseng.

The effects of *Panax* ginseng have been studied in regards to multiple CYP activities *in vitro*. The studies have focused on both whole ginseng extracts as well as the individual ginsenosides. In human recombinant enzymes, *Panax* ginseng was shown to inhibit CYP1A1 via competitive inhibition, and CYP1A2 and CYP2B1 via linear-mixed inhibition (Chang et al., 2002). Interestingly, in the previous study, the effects appeared to not be due to the individual ginsenosides tested. The individual ginsenosides have been shown to be inhibitors of CYP2C9 and CYP3A4 *in vitro* (He and Edeki, 2004; Liu et al., 2006b). Finally, ginseng extracts (500 μg/mL) did not cause a significant increase in CYP3A4 mRNA in primary human hepatocyte cultures.

Results from clinical trials with various ginseng extracts appear to be conflicting. Multiple reports conclude that there is a significant decrease in the anti-coagulant effect of warfarin in human volunteers who are also being administered a regimen of *Panax* ginseng (Janetzky and Morreale, 1997; Rosado, 2003). Another study, however, claims that no pharmacokinetic or pharmacodynamic effects on warfarin were noted when co-administered with *Panax ginseng* (Hu et al., 2005).

Goldenseal

One of the more popular uses for alternative medicines is to enhance the immune system. Goldenseal (*Hydrastis canadensis)* is a popular immunostimulant that includes various isoquinoline alkaloids such as berberine, hydrastine and hydrastinine (Chatterjee and Franklin, 2003). It has also been indicated as an antimicrobial and digestion aid. Of notable interest for drug interactions, the alkaloids mentioned above all contain a methylenedioxyphenyl moiety, a group which has been implicated in time-dependent CYP inhibition (Murray, 2000).

The components of goldenseal have shown inhibition and inactivation of CYP isoforms *in vitro*. The complete extract showed noncompetitive inhibition of CYP3A4-catalyzed testosterone 6β-hydroxylation with a K_i of approximately 0.11% extract. The individual alkaloids also inhibited CYP activity. Berberine inhibited CYP2D6-catalyzed 1'-hydroxybufuralol formation and 6β-hydroxytestosterone formation with IC_{50} values of 45 and 400 μM, respectively. Hydrastine inhibited CYP2D6 and CYP3A4 activities with IC_{50} values of approximately 350 and 30 μM, respectively. Hydrastine exhibited mechanism-based inhibition of CYP3A4 activity and formed MI complexes with expressed CYP2C9, CYP2D6 and CYP3A4 (Chatterjee and Franklin, 2003). It has been demonstrated that metabolism at the methylenedioxy moiety may produce a carbine intermediate that forms a quasi-irreversible bond with the prosthetic heme iron termed a metabolite-intermediate complex. Golden-seal extracts were also able to affect the activity of CYP3A4 in a Caco-2 cell system (Budzinski et al., 2007).

The *in vitro* inhibition noted above has also been observed *in vivo*. In clinical trials with 12 healthy volunteers, a significant inhibition of CYP2D6 and CYP3A4/5 activities as measured by debrisoquine urinary recovery ratios and 1'-hydroxymidazolam to midazolam serum ratios was observed (Gurley et al., 2005b).

Grapefruit Juice (and other Fruit Juices)

One widely studied natural product with regard to CYP-based drug interactions is grapefruit juice. Grapefruit juice has been shown to be a potent inhibitor of intestinal CYP3A4, though hepatic CYP3A4 appears to be unaffected (Lown et al., 1997; Bailey et al., 1998a; Bailey et al., 1998b). It has also been shown that the percent inhibition caused by grapefruit juice can vary from one source to the next. Because of the potential to interact with drugs that are metabolized by CYP3A4, the U.S. Food and Drug Administration (FDA) now requires many of these drugs to carry a precautionary label warning of the potential dangers of consuming these drugs with grapefruit juice (FDA, 2007).

Furanocoumarins are perhaps the best characterized source of herbal-mediated DDIs and produce what is known as the "grapefruit juice effect". *In vitro*, grapefruit juice has been shown to be a potent inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2D6 and CYP3A4 (Hukkanen et al., 2006; Girennavar et al., 2007). Two of the most abundant (and most studied) furanocoumarins are bergamottin and 6',7'-dihydroxybergamottin. In human intestinal microsomes, bergamottin exhibited substrate-dependent reversible inhibition of CYP3A4 (K_i, midazolam = 13.1 μM; K_i, testosterone = 1.6 μM) while the dihydroxybergamottin derivative had a K_i value that was approximately 0.8 μM for both CYP3A4 probes (Kakar et al., 2004).

Bergamottin is also a mechanism-based inactivator of CYP3A4, with K_I and k_{inact} values of 7.7 μM and 0.3 min^{-1} (He et al., 1998). The predominant mechanism of inactivation was suggested to be modification of the apoprotein, as over 90% of the heme but less than 50% of the apoprotein was recovered from an *in vitro* incubation.

In addition to grapefruit juice, a number of other fruit juices have been reported to cause drug interactions. Juices such as pomegranate, black mulberry, wild grape, and black raspberry have all shown drug interactions *in vitro* (Hidaka et al., 2005; Kim et al., 2006). In the study by Kim et al., the IC_{50} values for all of the fruit juices tested decreased upon pre-incubation, indicating a potential time-dependent component to the drug interaction.

Green Tea

Green tea (*Camellia sinensis)* is a commonly used herbal tea that has been reported to have antioxidant, anticancer and anti-inflammatory properties as well as to promote weight loss (Yang et al., 1998; Dulloo et al., 1999; Wang and Tian, 2001; Zhong et al., 2002). The pharmacological effects of green tea have been assigned to the flavanoids (or catechins) that are found in the tea (Mirkov et al., 2007).

In human liver microsomes, green tea was shown to inhibit CYP2C9-catalyzed tolbutamide 4-hydroxylation (IC_{50} = 57 μg/mg protein), CYP2D6-catalyzed bufuralol 1'-hydroxylation (IC_{50} = 50 μg/mg protein) and CYP3A4-catalyzed testosterone 6β-hydroxylation (IC_{50} = 63 μg/mg protein) (Nishikawa et al., 2004). Furthermore, addition of catechins from green tea to human liver microsomes inhibited the CYP3A4-catalyzed oxidation of irinotecan and UGT1A1-catalyzed glucuronidation of its SN-38 metabolite (Mirkov et al., 2007). When the catechins were assessed for inductive effects in human hepatocytes, no induction of CYP3A4 was noted.

A single study in healthy volunteers showed that green tea did not alter CYP2D6 (dextromethorphan demethylation) or CYP3A4 (alprazolam hydroxylation) activity after consumption of green tea for 14 days (Donovan et al., 2004a). Similarly, CYP1A2 and CYP2C19 were also unaffected (Chow et al., 2006).

Kava

Kava (*Piper methysticum)* is a shrub found mostly in the South Pacific that is often used to treat insomnia, anxiety or as a general relaxant. A significant amount of research has focused on the uses, components and drug interactions of kava extract in recent years. Kava gained increasing notice when cases of liver failure and skin dermopathy were reported (Keledjian et al., 1988; Strahl et al., 1998; Kraft et al., 2001). The primary constituents of kava extract are kavalactones, including yangonin, desmethoxyangonin, methysticin, 7,8-dihydromethysticin, kawain, and 7,8-dihydrokawain and account for the majority of the lipid soluble components from kava (Lebot and Levesque, 1989; Mathews et al., 2002).

Additional research has focused on drug interactions that are caused by kava extract and the individual components isolated from the extract. In human liver microsomes, whole kava extract resulted in significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Mathews et al., 2002; Mathews et al., 2005; Jeurissen et al., 2007). Inhibition of various CYP activities was also noted for desmethoxyangonin (CYP2C9 and CYP3A4), methysticin (CYP2C9, CYP2D6 and CYP3A4), and 7,8-dihydromethysticin (CYP2C9, CYP2C19 and CYP3A4). Both methysticin and 7,8-dihydromethysticin formed MI complexes (both compounds contain a methylenedioxyphenyl group) following pre-incubation with NADPH. Finally, kava has also been shown to be an inducer of CYP3A4 mRNA in human hepatocytes, where pre-treatment of the cells with kava resulted in a 386 ± 185% increase in mRNA levels versus control (Raucy, 2003).

While reports vary on the potential of kava to cause *in vivo* drug interactions, a significant interaction has been reported for kava when co-administered with alprazolam, a CNS depressant and CYP3A4 substrate (Almeida and Grimsley, 1996). Similar reports have been issued for the possible interaction of kava with barbiturates, benzodiazepines and alcohol (Blumenthal, 1998; DerMarderosian and Beutler, 1999).

Licorice

Licorice root (*Glycyrrhiza uralensis)*, long known as an effective expectorant, has also been used to treat mouth ulcers, irritable bowel syndrome, Crohn's disease and as a mild laxative (Maimes and Winston, 2007). Excessive use of licorice has been shown to be toxic to both the liver and cardiovascular system and may also result in hypertension and edema.

In vitro, the extract from licorice root was shown to be an inhibitor of CYP3A4 in human recombinant enzymes with an IC_{50} value of 0.022 mg/mL (Tsukamoto et al., 2005b). Of the individual

components of licorice that were tested, licopyranocoumarin, liquirtin and liquirtine apioside were found to be the major contributors to the observed inhibition of CYP3A4. In addition, the isoflavan glabridin was shown to be a competitive inhibitor of CYP2C9 (Kent et al., 2002).

Polyphenolic compounds may be precursors of quinones or quinone methide intermediates that are known to inactivate CYPs. The licorice root isoflavan glabridin inactivates CYP3A4 and CYP2B6. Loss of CYP3A4 activity was correlated with loss of the CYP-reduced CO spectrum, while minimal loss of the CYP-reduced CO spectrum was observed with CYP2B6, suggesting differential mechanisms for inactivation. While the mechanism of inactivation for CYP3A4 was not determined, methylation of the polyphenol moiety eliminated inactivation of CYP3A4.

Luteolin

Luteolin is an emerging herbal therapy thought to have anti-oxidant, radical scavenging, anti-cancer and anti-inflammatory properties. It is commonly found in many edible fruits and vegetables and is also sold as an herbal supplement. One recent study found that of the many commonly occurring flavonoids, luteolin was one of the most potent against carcinoma of the stomach, cervix and bladder (Cherng et al., 2007).

While little data is available as to the drug interaction potential is available, one recent report by Foti et al. explored the inhibition of CYP activity by luteolin as part of an herbal remedy containing multiple herbal components. In human liver microsomes, luteolin appeared to be a potent inhibitor of CYP2B6-catalyzed bupropion hydroxylation, CYP2C9-catalyzed 4-hydroxytolbutamide formation and CYP2D6-catalyzed dextrorphan formation (Foti et al., 2007). Luteolin has also been shown to be an inducer of CYP3A4 activity via interaction with PXR in HepG(2) cells (Liu et al., 2006a).

Methoxypsoralen

8-methoxypsoralen is an antimicrobial furanocoumarin that is found in parsnips, barley, celery and other plant species (Miyazaki et al., 2005). It is also indicated in photochemotherapy regimens, where it has been shown to be effective in the treatment of psoriasis (Glew, 1979).

In vitro, 8-methoxypsoralen was shown to be an inhibitor of CYP2A6, and a structure of the compound complexed to the enzyme has been published (Yano et al., 2005). It is also known to be a mechanism based inactivator of CYPs, in this case CYP2A6 and CYP2B1. (Koenigs et al., 1997). Characterization of glutathione metabolites isolated from *in vitro* incubations of 8-methoxypsoarlen suggest that a furanoepoxide intermediate may be involved in CYP inactivation.

Milk Thistle

Silybum marianum, an herbal remedy more commonly known as milk thistle, has traditionally been used to treat a number of liver disorders (Flora et al., 1998). To date, it is one of the most widely used herbal medications (Venkataramanan et al., 2000; Hu et al., 2005). It is also known to protect the liver against acetaminophen, thioacetamide, D-galactosamine, amanitin and carbon tetrachloride (CCl_4) mediated hepatotoxicity (Vogel et al., 1984; Mourelle et al., 1989; Muriel et al., 1992; Chrungoo et al., 1997). The active ingredients in milk thistle are primarily flavonoligans, components that are formed *via* the radical coupling of a phenylpropanoid and a flavanoid (Dewick 1997). The flavonoligans are present as multiple structural isomers, collectively referred to as silymarin.

Milk thistle has been evaluated both *in vitro* and *in vivo* for potential drug interactions. In human hepatocyte cultures, the addition of 0.1 and 0.25 mM silymarin inhibited CYP3A4 activity by approximately 50 and 100%, respectively (Venkataramanan et al., 2000). A similar down regulation of CYP3A4 activity was observed in a Caco-2 cell monolayer system (Budzinski et al., 2007). Additionally, in human recombinant CYP preparations, silybin (the primary isomer of the silymarin group of isomers) showed time-, concentration- and NADPH-dependent inactivation of CYP2C9 and CYP3A4 (Sridar et al., 2004).

In vivo drug interactions have not been as pronounced as those observed *in vitro*. Clinical trials in healthy volunteers with digoxin and indinavir did not reveal any clinically significant alteration of drug metabolizing enzyme activity in these trials (Piscitelli et al., 2002; DiCenzo et al., 2003; Gurley et al., 2006b). Similarly, a study designed to assess the effects of milk thistle on irinotecan pharmacokinetics in healthy volunteers reveals no significant risk of drug interactions *in vivo* (van Erp et al., 2005).

Resveratrol

Resveratrol (3,4',5-trihydroxy-trans-stilbene) is a polyphenolic constituent of red wine, grapes and

peanuts. It is also found in a number of plants and fruits, including raspberries, blueberries, cranberries and some species of pine trees. It reportedly has many positive activities, including antioxidant, cardio-protective and anti-inflammatory effects.

In vitro, resveratrol has been shown to be a potent inhibitor of CYP1A1 and CYP1A2, albeit to a lesser extent (Chun et al., 1999). Naturally occurring analogues of resveratrol were also shown to be inhibitors of CYP1A2, as well as CYP2E1 (Mikstacka et al., 2006). Resveratrol also inactivates CYP3A4 in a time dependent manner, with K_I and k_{inact} values of 20 μM and 0.20 min^{-1} (Chan and Delucchi, 2000). CYP3A4-mediated epoxidation and subsequent *p*-benzoquinone methide formation has been proposed as the mechanism of inactivation by resveratrol.

Saw Palmetto

Saw palmetto (*Serenoa repens)* is becoming an increasingly popular herbal remedy for the treatment of benign prostatic hypertrophy and chronic cystitis (Tracy and Kingston, 2007), though recent studies challenging this notion have found that saw palmetto was no more effective than placebo in combating benign prostatic hypertrophy (Bent et al., 2006). The active ingredients of saw palmetto are fatty acids, plant sterols and flavonoids (Gordon and Shaughnessy, 2003).

In vitro, saw palmetto was shown to be a potent inhibitor of CYP2C9, CYP2D6 and CYP3A4 activity (Yale and Glurich, 2005). *In vivo*, however, two independent studies have shown no effect of saw palmetto on the marker activities of CYP1A2, CYP2D6, CYP2E1 or CYP3A4 (Markowitz et al., 2003b; Gurley et al., 2004).

Schisandra Fruit

Schisandra fruit (*Schisandra chinensis)* is used for sedation and antitussive effects, improved liver health and as an overall tonic. It is often used as a component of more complex mixtures, such as Japanese Kampo medicines or in combination with other herbal remedies.

In vitro experiments utilizing human liver microsomes have identified potent CYP3A4 inhibitors in the schisandra fruit extract (Iwata et al., 2004). The individual schizandrin and gomisin components of the extract were assessed for CYP3A4 inhibition. While the schizandrin compounds showed no appreciable inhibition, IC_{50} values for the gomisin group ranged from 0.257 to 6.71 μM against CYP3A4 (6β-hydroxy-testosterone activity).

Herbal components containing methylenedioxy moieties may also exhibit time-dependent inhibition of CYPs. Extracts from the schisandra fruit containing this functional group were found to be potent inhibitors of CYP3A4. The most potent component, gomisin C, was also found to be a mechanism based inactivator of CYP3A4. Rise in a diagnostic peak at 455 nm is indicative of MI complex formation and was observed in incubations containing gomisin C (Iwata et al., 2004).

Soy

Soy-derived products are often used to treat symptoms of menopause in women. The primary effects of soy are usually attributed to a number of isoflavones that have been isolated, namely daidzein and genistein. It has also been claimed that diets rich in soy can reduce cholesterol levels (Song et al., 2007).

In vitro, various components of soy have been shown to have inhibitory activity against the CYP enzymes. In particular, the isoflavones daidzein, genistein and glycitein were all uncompetitive inhibitors of CYP2A6 in a baculovirus-expressed enzyme system (Nakajima et al., 2006). In human liver microsomes, hydrolyzed soy extracts also were inhibitors of CYP2C9 and CYP3A4 (Anderson et al., 2003). *In vivo*, no effect was observed on the 6β-hydroxycortisol to cortisol ratio, indicating that soy extract was probably not a clinically relevant inducer of CYP3A4 activity *in vivo*.

St. John's Wort

One of the more widely used and researched alternative medicines in recent years has been St. John's wort (*Hypericum perforatum)*. It is most commonly used for the treatment of mild to moderate depression (Linde et al., 1996; Wheatley, 1997; Shelton, 2002). While the extract is a mixture of multiple biologically actively compounds, hypericin and hyperforin are two of the main constituents. Hyperforin is also the main pharmacological component that is responsible for the herbal remedy's anti-depressant qualities, owing to it being a potent serotonin, norepinephrine and dopamine reuptake inhibitor (Chatterjee et al., 1998; Moore et al., 2000).

Aside from its pharmacologically active properties, a large amount of recent research has also focused on the potential of St. John's wort to cause drug interactions both *in vitro* and *in vivo*. Complex drug

interactions can arise from other drugs that are co-administered with St. John's wort owing to the herb's ability to both inhibit and induce CYP enzymes. Crude extracts of St. John's wort have been shown to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in cDNA expressed enzymes (Obach, 2000). When the individual components were extracted, both hyperforin and I3,II8-biapigenin exhibited potent inhibition of the CYP enzymes noted above. A more recent study has shown that the individual components furoadhyperforin and furohyperforin were actually more potent inhibitors of CYP3A4 than hyperforin (Lee et al., 2006a). In human hepatocytes, exposure of the cells to hyperforin resulted in an increase in mRNA, protein and activity levels of CYP3A4 and CYP2C9 (Komoroski et al., 2004). No effect was observed on CYP1A2 or CYP2D6 and similar experiments using hypercin did not result in any significant levels of induction. The inductive effects of St. John's wort have been explained by the fact that hyperforin is also a ligand for the pregnane X receptor (PXR), an orphan nuclear receptor that regulates levels of many of the CYP enzymes (Moore et al., 2002).

Numerous clinical trials have also been undertaken to understand the *in vivo* drug interactions that may be attributable to St. John's wort. Multiple studies have shown that prolonged usage of St. John's wort can induce both hepatic and intestinal CYP3A4 (Gurley et al., 2002; Bauer et al., 2003; Dresser et al., 2003). In general, studies have also shown that short term usage (less than 8 days) had no significant effects on CYP3A4 activity *in vivo* (Ereshefsky et al., 1999). Induction of CYP2E1, though to a lesser extent (28%), was observed for CYP2E1 (Gurley et al., 2005a).

Usnic Acid

Usnic acid, a metabolite found in various lichen species, has had a wide number of therapeutic uses. These have included use as an antibiotic, antiviral, anti-oxidant, analgesic, cosmetic, and more recently, as a weight loss aid. Currently, there are no clinical trials that support any of these claims in humans (Frankos, 2005). Usnic acid came to the attention of the FDA in the 1990s, when reports began to surface surrounding the incidence of liver problems in those patients taking usnic acid containing supplements (Arneborn et al., 2005; Frankos, 2005; Sanchez et al., 2006).

A recent study investing the metabolism and drug interactions of usnic acid found the supplement to be a very potent inhibitor of the CYP2C family of enzymes in human liver microsomes. IC_{50} values ranged from 0.009 μM for CYP2C19 to 6.3 μM for CYP2C18, with the IC_{50} for CYP2C8 and CYP2C9 being 1.9 μM and 0.094 μM, respectively (Foti et al., 2008). An extrapolation of the in *vitro* data using SimCYP® showed a significant risk of drug interactions with other drugs that are cleared primarily by CYP2C enzymes.

Valerian

Valerian (*Valeriana officinalis)* is another widely used herbal remedy in the United States. Its major use is for sedation and/or hypnosis, though clinical trials assessing its efficacy in treating insomnia have been inconclusive (Stevinson and Ernst, 2000; Krystal and Ressler, 2001; Sparreboom et al., 2004). The main components of valerian that have been isolated include derivatives of valerenic acid, valepotriates, alkaloids, furanofuran lignans and free amino acids (Houghton, 1999).

Extracts from the valerian root have been shown to inhibit CYP3A4 activity *in vitro* (Lefebvre et al., 2004; Sparreboom et al., 2004). Organic extracts of the root showed as high as 88% inhibition of CYP3A4 activity in a fluorescence-based assay. Individual components such as valerenic acid showed a much lower inhibitor potential against CYP3A4 and minor inhibition of CYP2C9 and CYP2C19 (Zhou et al., 2003; Sparreboom et al., 2004).

The effects of valerian on co-administered medications *in vivo* appear to be less significant than those observed *in vitro*. Studies designed to probe *in vivo* drug interactions between valerian and substrates for CYP3A4 or CYP2D6 have come back negative. Donavan et al. report minimal effects on CYP3A4 activity and no effect on CYP2D6 activity following 14 days of valerian administration (1 gram/day) (Donovan et al., 2004b). Gurley et al. report similar results following 375 mg/day of valerian for 28 days (Gurley et al., 2005b).

Wu-chu-yu Tang

The traditional Chinese herbal medicine Wu-chu-yu-tang is often used for treating migraines and/or cases of cold-related emesis (Kano et al., 1991). The herbal remedy actually contains a mixture of herbs, including Wu-chu-yu, ginseng, ginger, and tai-geui (Ueng et al., 2002a).

In vitro, CYP-mediated drug interactions with components of Wu-chu-yu tang have been observed. Rutaecarpine, a quinazolinocarboline alkaloid that has

been isolated from the herbal remedy, was shown to be a selective CYP1A2 inhibitor in human liver microsomes (Ueng et al., 2002b). The observed IC_{50} values for rutaecarpine against 7-methoxyresorufin and 7-ethoxyresofufin activities in human liver microsomes were 0.05 and 0.03 μM, respectively. In addition, a number of CYP isoforms (CYP1A2, CYP2D6 and CYP3A4) are known to be involved in the metabolism of rutaecarpine to multiple hydroxylated metabolites. In particular, 10-hydroxyrutaecarpine was shown to inhibit CYP1A1, CYP1A2 and CYP1B1 with IC_{50} values of 2.56, 2.57 and 0.09 μM, respectively (Ueng et al., 2006). Thus the potential for both reversible and time-dependent inhibition exists for components of Wu-chu-yu tang *in vitro*.

CONCLUSION

As the use of complimentary and alternative medicines continues to increase around the world, the ability to predict and ultimately avoid adverse reactions with these therapies takes on a new found importance. Multiple reports continue to emerge documenting the ability of herbal medicines to contribute to drug interactions involving both the cytochrome P450 family of enzymes as well as other enzymes not covered in this review (i.e., UDP-glucuronosyltransferases, esterases, etc.). In addition to increasing the amount of research pertaining to herbal remedies, the need to ensure that this information is properly disseminated at the consumer level is also key to avoiding potentially harmful interactions. Finally, this information combined with an increased awareness on the part of physicians and pharmacists should help to alleviate some of the risks associated with herbal remedies while still allowing patients to realize the beneficial aspects of alternative medicine.

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