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Pharmacokinetic interactions of drugs with St John's wort

Shufeng Zhou *Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore.*

Eli Chan *Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore.*

Shen-Quan Pan *Department of Biological Sciences, Faculty of Science, National University of Singapore, Singapore.*

Min Huang *Institute of Clinical Pharmacology, School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510089, PR China.*

Edmund Jon Deoon Lee *Department of Pharmacology, Faculty of Medicine, National University of Singapore, Singapore.*

Abstract

There is a worldwide increasing use of herbs which are often administered in combination with therapeutic drugs, raising the potential for herb–drug interactions. St John's wort (*Hypericum perforatum*) is one of the most commonly used herbal antidepressants. A literature search was performed using Medline (via Pubmed), Biological Abstracts, Cochrane Library, AMED, PsycINFO and Embase (all from their inception to September 2003) to identify known drug interaction with St John's wort. The available data indicate that St John's wort is a potent inducer of CYP 3A4 and P-glycoprotein (PgP), although it may inhibit or induce other CYPs, depending on the dose, route and duration of administration. Data from human studies and case reports indicate that St John's wort decreased the blood concentrations of amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, methadone, midazolam, nevirapine, phenprocoumon, simvastatin, tacrolimus, theophylline and warfarin, whereas it did not alter the pharmacokinetics of carbamazepine, dextromethorphan, mycophenolic acid and pravastatin. St John's wort decreased the plasma concentration of the active metabolite SN-38 in

cancer patients receiving irinotecan treatment. St John's wort did not alter the pharmacokinetics of tolbutamide, but increased the incidence of hypoglycaemia. Several cases have been reported that St John's wort decreased cyclosporine blood concentration leading to organ rejection. St John's wort caused breakthrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives. It also caused serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors (e.g. sertraline and paroxetine). Both pharmacokinetic and pharmacodynamic components may play a role in these interactions. Because the potential interaction of St John's wort with other drugs is a major safety concern, additional systematic research on herb–drug interactions and appropriate regulation in herbal safety and efficacy is needed.

Keywords

cytochrome P450, drug interactions P-glycoprotein, St John's wort

Introduction

There is a worldwide increasing use of herbs which are often administered in combination with therapeutic drugs, raising the potential for herb–drug interactions. Pharmacokinetic herb–drug interactions arise through altered absorption, metabolism, distribution and/or excretion of drugs. Frequently, the underlying mechanism of altered drug concentrations by concomitant herbal medicines is either induction or inhibition of hepatic and intestinal drug-metabolizing enzymes [in particular, cytochrome P450s

(CYP)], and/or of drug transporters such as P-glycoprotein (PgP) (Walter-Sack and Klotz, 1996; Wilkinson, 1997; Evans, 2000; Ioannides, 2002; Zhou *et al.*, 2003). The interplay of both intestinal PgP and CYP3A4 determines bioavailability of many drugs. Thus, the modulation of intestinal PgP and CYP3A represents an important mechanism for the enhanced or reduced bioavailability of coadministered drugs. Furthermore, combined use of herb with drug may mimic, increase, or reduce the effects of either interacting compound, resulting in clinically important herb–drug interactions (Fugh-Berman, 1999, 2000; Fugh-Berman and Ernst, 2001;

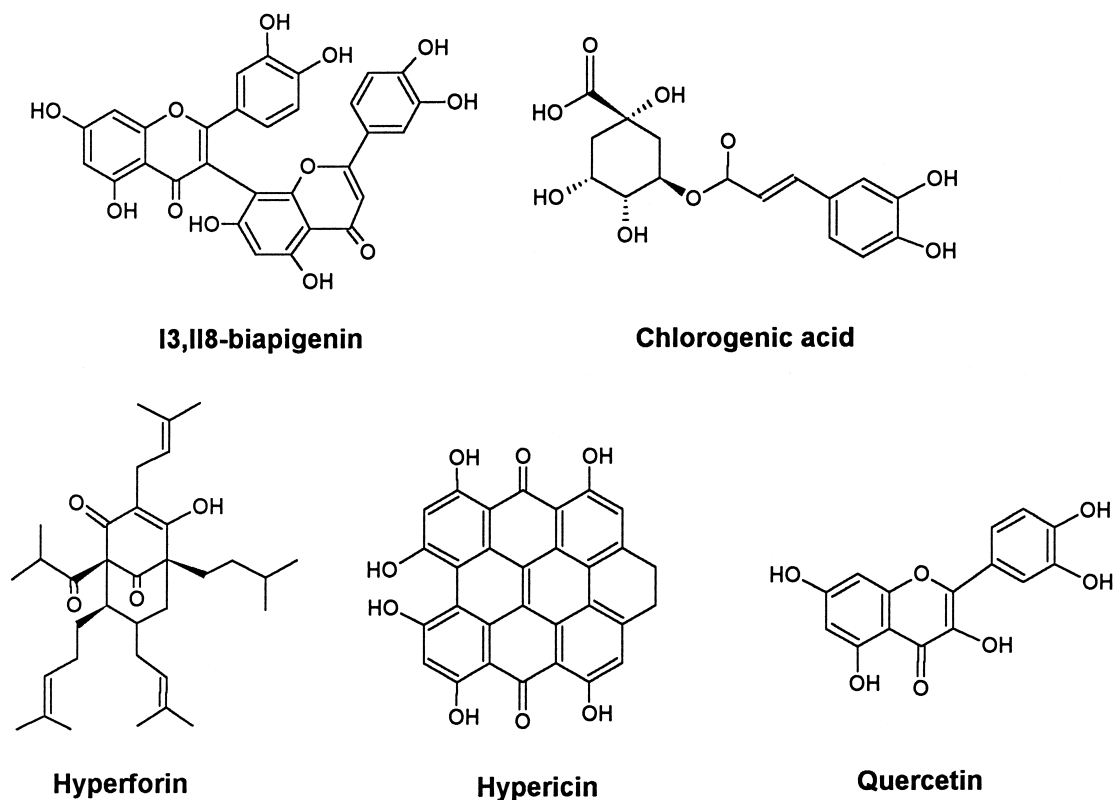


Figure 1 Chemical structures of the major constituents of *St John's wort*

Izzo and Ernst, 2001). Synergistic therapeutic effects may lead to unfavourable toxicities and complicate the dosing regimen of long-term medications, while antagonistic interactions will result in decreased efficacy and therapeutic failure.

St John's wort (*Hypericum perforatum*) is one of the most commonly used herbal medicines for the treatment of depression (Di Carlo *et al.*, 2001; Bilia *et al.*, 2002; Schulz, 2002). *St John's wort* is a complex mixture of over two dozen constituents, including flavonols, flavonol glycosides, biflavones, naphthodianthrones, acylphloroglucinols and phenylpropanes (Fig. 1) (Erdelmeier, 1998; Obach, 2000). Among these, hyperforin is the major constituent responsible for its antidepressant activity because it inhibits the reuptake of neurotransmitters (e.g. serotonin, noradrenaline and dopamine) in synapses (Moore *et al.*, 2000). Due to the extensive use and concern of drug interactions, the effects of *St John's wort* on the pharmacokinetics and pharmacodynamics of some clinically important drugs have been investigated in humans. In addition, spontaneous reports and published case reports provide supportive evidence for the interactions of *St John's wort* with certain drugs. This review highlights the reported drug interactions with *St John's wort*, with an emphasis on the possible underlying mechanisms and clinical outcomes.

Literature search

The literature was reviewed to identify all pertinent case reports, case series and animal and human studies. A literature search was performed using the following databases: Medline (via Pubmed), Biological Abstracts, PsycINFO, Cochrane Library, *AMED (Allied and Complementary Medicine)*, *Biosis Previews* and Embase (all from their inception to September 2003). In addition, a number of Chinese journals related to herbal studies were searched manually from the first publication date onwards. The terms used included *St John's wort*, hyperforin, hypericin, hypericum, herb, CYP, P-gP and drug interactions. All animal and human studies performed *in vitro* and *in vivo* relating to the drug interactions with *St John's wort* were included. Human studies including case reports, case series, clinical trials or other types of studies, were all included.

Effects of *St John's wort* on CYPs and P-gP

Effects on CYPs

The CYP superfamily, containing 57 genes (Nelson, 2003), contributes to the metabolism of a variety of xenobiotics including

therapeutic drugs, carcinogens, steroids and eicosanoids (Gonzalez, 1990; Nelson *et al.*, 1996; Rendic and Di Carlo, 1997; Nebert and Russell, 2002; Rendic, 2002). The relative abundance of the hepatic CYPs in humans has been determined as: CYP1A2 (13%), 2A6 (4%), 2B6 (< 1%), 2C (20%), 2D6 (2%), 2E1 (7%) and 3A4 (30%) (Shimada *et al.*, 1994; Rendic and Di Carlo, 1997). Consistently, the significance of the individual CYP enzyme in human drug metabolism varies, with CYP3A, CYP2D and CYP2C being responsible for the metabolism of 50%, 25% and 20%, respectively, of the currently known drugs (Bertz and Granneman, 1997; Rendic and Di Carlo, 1997). All CYPs are subject to induction and inhibition by exposure to a wide variety of xenobiotics including various herbs. Herb–drug interactions can frequently arise when drugs and herbs are coadministered, and the herb modulates the metabolic clearance of the drug by inhibition or induction of a specific CYP enzyme (Zhou *et al.*, 2003).

Studies performed *in vitro* have demonstrated that St John's wort extract is a potent inducer of CYP2B6 and 3A4, and the responsible constituent is hyperforin (Moore *et al.*, 2000; Wentworth *et al.*, 2000; Goodwin *et al.*, 2001). Hyperforin, but not hypericum extracts, resulted in a marked induction of CYP3A4 expression after treatment of primary human hepatocytes. Studies performed *in vitro* have shown that hyperforin is a potent ligand ($K_i = 27$ nmol) for the pregnane X receptor (Moore *et al.*, 2000), which is an orphan nuclear receptor regulating the expression of CYP2B6 and 3A4 (Durr *et al.*, 2000; Wentworth *et al.*, 2000; Goodwin *et al.*, 2001). CYP2B6, CYP3A4 and MDR1 genes have transcriptional binding sites for the pregnane X receptor (Kliwer *et al.*, 1998; Geick *et al.*, 2001; Goodwin *et al.*, 2002). Binding of a ligand to this receptor increases transcription of these genes with cognate recognition sites in their 5'-regulatory region. The induction of drug metabolizing enzymes by St John's wort is selective, and enzymes such as CYP1A2 and 2D6 are not induced (Wang *et al.*, 2001). The induction by St John's wort occurs locally in the intestine following oral administration and intestinal absorption of inducing agents and also in the liver (Wang *et al.*, 2001; Dresser *et al.*, 2003).

St John's wort extracts and its major constituents have been reported to inhibit the activities of recombinant CYP1A2, 2C9, 2C19, 2D6 and 3A4 (Obach, 2000). Different inhibitory potency and mechanism for various CYPs have been observed with individual constituents of St John's wort. The flavonoid I3,II8-biapi-genin is a potent competitive inhibitor of CYP3A4, CYP2C9, and CYP1A2 ($K_i = 0.038, 0.32,$ and 0.95 μM , respectively); whereas hyperforin is a potent noncompetitive inhibitor of CYP2D6 activity with a K_i of 1.5 μM and a competitive inhibitor of CYP2C9 and CYP3A4 activities ($K_i = 1.8$ and 0.48 μM , respectively) (Obach, 2000). Hypericin competitively inhibited CYP2C9, 2D6 and 3A4 with K_i values of 1.4 – 4.2 μM . A similar K_i value (3.3 μM) was observed with quercetin for CYP1A2 (Obach, 2000). However, quercetin just moderately inhibited CYP2C9, 2D6 and 3A4, with IC_{50} values > 20 μM . Hyperforin was a weak or moderate inhibitor for CYP1A2 ($\text{IC}_{50} > 100$ μM) and 2C19 ($\text{IC}_{50} = 31$ μM). Chlorogenic acid exhibited little inhibitory effects on CYP1A2, 2C9, 2C19, 3D6 and 3A4.

A drug interaction occurring *in vivo* is likely if $[I]/K_i > 0.2$, where $[I]$ is the maximum unbound plasma concentration (Ito *et al.*, 1998). The maximum plasma concentration (C_{max}) of hyperforin is 0.17 – 0.50 μM in humans following a single dose (300 mg) of standardized hypericum extracts containing 5% hyperforin (Biber *et al.*, 1998; Agrosi *et al.*, 2000). Thus, an $[I]/K_i$ of 0.35 – 1.04 for CYP3A4, 0.11 – 0.33 for CYP2C9 and 0.09 – 0.28 for CYP2D6 would be expected. This would raise the potential for drug interactions with a number of substrates of these CYP enzymes. These include amitriptyline and dextromethorphan (CYP2D6), warfarin, tolbutamide and phenprocoumon (CYP2C9), and HIV protease inhibitors, midazolam, oral contraceptives and cyclosporine (CYP3A4). On the other hand, the C_{max} of hypericin was 0.03 – 0.15 μM after the administration of 300 mg hypericum extracts containing 0.3% hypericin (Staffeldt *et al.*, 1993, 1994; Chi and Franklin, 1999). Therefore, the $[I]/K_i$ ratio will fall to 0.01 – 0.04 which is much lower than 0.2, suggesting that hypericin alone appeared not to alter the metabolism of substrates of CYP2D6, 2C9 and 3A4. It should be noted that the potential for inhibition *in vivo* depends not only on the inhibitory potency (K_i), but also on the overall disposition properties of the inhibitor (e.g. the extent of its intestinal absorption and plasma protein binding, uptake into the liver and clearance). More importantly, in the case of a complex mixture of compounds such as herbs, the relative abundance of each compound in the preparation would also have an impact on identifying the constituent most responsible for herb–drug interactions.

Animal studies using probe drugs indicate that St John's wort modulates various CYP enzymes, depending on herbal dose and regimen. Short-term treatment (4 days) of St John's wort extract (435 mg/kg/day), hypericin (1 mg/kg/day) or hyperforin (10 mg/kg/day) did not alter the activities of mouse CYP1A, 2E1 and 3A4 (Bray *et al.*, 2002). However, administration of St John's wort extract (140 or 280 mg/kg/day) to the mouse for 3 weeks resulted in a two-fold increase in both the CYP3A and 2E1 activities, but no effect on CYP2E1 activity despite the 2.6-fold increase in its protein level (Bray *et al.*, 2002). The protein level of CYP3A was also increased six-fold, but the CYP1A protein level remained unchanged. In addition, the administration of St John's wort extract to rats at 1000 mg/kg/day for 14 days resulted in a significant increase in hepatic CYP3A2 protein expression (Durr *et al.*, 2000).

In healthy subjects, St John's wort is an inducer of CYP3A4 as demonstrated by a significantly increased urinary 6 β -hydroxycortisol/cortisol ratio (Roby *et al.*, 2000) and midazolam clearance (Wang *et al.*, 2001; Dresser *et al.*, 2003). Clinical studies using a probe drug cocktail indicated that long-term (2 weeks) St John's wort administration at 900 mg significantly induced intestinal and hepatic CYP3A4, but did not alter the activities of CYP2C9, 1A2 and 2D6 when the probe substrates [tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6)] were used (Roby *et al.*, 2000; Wang *et al.*, 2001). However, short-term administration (3–4 days) of St John's wort at the same dose had no effect on CYP3A4 (alprazolam and midazolam as substrates) and 2D6 (dextromethorphan as substrate) activity in human volunteers (Markowitz *et al.*, 2000; Wang *et al.*, 2001). This suggests that induction rather

than stimulation is the mechanism underlying these interactions. Alprazolam also has minimal first-pass elimination.

Animal and human studies performed *in vitro* and *in vivo* have indicated that St John's wort contains both inhibitory and activating constituents for the CYP system, causing temporally distinguishable inhibition and induction. The effects of St John's wort on CYPs may be species- and tissue-specific, depending on the dose, route and duration of administration, and formulation as well as the source of the herb. Consequently, this will result in some difficulty in predicting the potential for St John's wort to cause clinically important drug interactions based on animal and human studies performed *in vitro*. Further studies are required, particularly investigation of the effects of prolonged exposure of St John's wort on the activities of the different enzymes.

Effects on Pgp

Pgp is a 170-kDa plasma glycoprotein encoded by the human *MDR1* gene. It is expressed constitutively in a number of normal tissues and is found at high levels on the apical surfaces of epithelial cells in the liver (bile canaliculi), kidney (proximal tubule), pancreas (pancreatic ductal cell), small intestine and colon (columnar mucosal cell) and adrenal gland (Gottesman and Pastan, 1993; Chen *et al.*, 1996). Pgp is involved in drug absorption and elimination from various organs such as the intestine, liver, kidney and brain (Ambudkar *et al.*, 1999; Yu, 1999; Lin and Yamazaki, 2003). Thus, modulation of Pgp by xenobiotics may alter the pharmacokinetics of coadministered drugs.

The magnitude of the drug interactions (e.g. digoxin) by St John's wort observed clinically is greater than that predicted by data obtained *in vitro*, suggesting that induction of CYP3A4 is unlikely to be the sole mechanism for the interactions and a second interaction mechanism should exist. Several studies indicate that St John's wort induces intestinal Pgp *in vitro* and *in vivo* (Durr *et al.*, 2000; Perloff *et al.*, 2001; Hennessy *et al.*, 2002). Treatment of LS-180 intestinal carcinoma cells with St John's wort or hypericin at 3–300 μ M caused a four to seven-fold increase in the expression of Pgp (Perloff *et al.*, 2001). Cells chronically treated with St John's wort had decreased accumulation of rhodamine 123. Direct evidence for induction of Pgp by St John's wort *in vivo* is provided by findings that long-term pre-treatment increased MDR1 expression in the rat intestine (Durr *et al.*, 2000) and also human peripheral blood lymphocytes (Hennessy *et al.*, 2002).

The administration of St John's wort extract to rats for 14 days resulted in a 3.8-fold increase of intestinal Pgp expression (Durr *et al.*, 2000). Oral administration of St John's wort at 900 mg/day for 14 days in healthy volunteers resulted in a 1.4-fold increase in Pgp expression (Durr *et al.*, 2000). The probe substrates of Pgp, fexofenadine and cyclosporine were found to have increased clearance in healthy subjects treated with St John's Wort at 900 mg/day for 2 weeks (Wang *et al.*, 2002; Dresser *et al.*, 2003). Moreover, chronic treatment with St John's wort (16 days) produced a 4.2-fold increase in expression of Pgp in the peripheral blood lymphocytes of healthy volunteers (Hennessy *et al.*, 2002). This was associated with enhanced drug efflux function, resulting in reduced intracellular accumulation of rhodamine.

Drugs that interact with St John's wort

Anticancer drugs

Irinotecan Irinotecan (CPT-11) is a potent DNA topoisomerase I inhibitor used in the treatment of advanced colorectal and lung cancer, giving an objective response in approximately 20% of treated patients (Canal *et al.*, 1996; Gupta *et al.*, 1997; Kudoh *et al.*, 1998). In an unblinded, randomized crossover study involving five cancer patients, it was found that treatment of St John's wort (900 mg/day, oral) for 18 days decreased the plasma levels of the active metabolite SN-38 by 42% (Mathijssen *et al.*, 2002). This was accompanied by a decreased myelosuppression. These findings indicate that patients on irinotecan treatment should refrain from taking St John's wort.

Anticonvulsants

Carbamazepine Intake of St John's wort at 900 mg/day for 2 weeks did not alter the pharmacokinetics of the antiepileptic drug carbamazepine in healthy subjects (Burstein *et al.*, 2000). Carbamazepine is mostly eliminated by metabolism (Pelkonen *et al.*, 2001). The predominant enzyme catalysing the metabolism of carbamazepine is CYP3A4, but other enzymes, such as CYP2C8, also make a substantial contribution (Kerr *et al.*, 1994). The lack of alteration of carbamazepine pharmacokinetics by St John's wort may be due to the presence of both CYP-inducing and CYP-inhibiting constituents in the same herbal formulation, carbamazepine's inducing effects on multiple CYPs (Kudriakova *et al.*, 1992; Tateishi *et al.*, 1999) and non-substrate of Pgp for carbamazepine (Owen *et al.*, 2001). It is noteworthy that another widely used herb, Saiko-ka-ryukotsu-borei-to extract powder, did not affect the pharmacokinetics of carbamazepine in rats (Ohnishi *et al.*, 2001).

Antidepressants

Amitriptyline Both St John's wort and amitriptyline have a high probability of concomitant use. Concomitant intake of the hypericum extract LI160 (900 mg daily) for at least 2 weeks in 12 depressed patients decreased the area under the plasma concentration–time curve (AUC) of amitriptyline (by 21.7%) and its demethylated metabolite, nortriptyline (by 40.6%) as well as of all its hydroxylated metabolites, except for 10-E-hydroxynortriptyline (Johns *et al.*, 2002). Plasma levels of amitriptyline and its hydroxylated metabolites were gradually decreased, whereas nortriptyline concentrations were already markedly decreased after 3 days of cotreatment with hypericum. Cumulative urinary amounts of amitriptyline and its metabolites decreased to the same extent as plasma concentrations upon hypericum comedication. The demethylation of amitriptyline to nortriptyline is primarily catalysed by CYP2C19 and 3A4 (Venkatakrishnan *et al.*, 1998, 2001). The further metabolism of nortriptyline through hydroxylation at the 10-position is mediated by CYP3A4 and 2D6 (Venkatakrishnan *et al.*, 1999). Thus, induction of CYP3A4 may have caused the decrease in the AUC of amitriptyline and nortriptyline. Physicians

should be aware of this interaction when treating patients with amitriptyline.

Selective serotonin reuptake inhibitors (SSRIs) SSRIs act by inhibition of the neuronal uptake pump for serotonin, a property shared with the tricyclic antidepressants, but without affecting the other various neuroreceptors or fast sodium channels (Vaswani *et al.*, 2003). Cases have been reported where combination of St John's wort with SSRIs caused symptoms characteristic of central serotonergic syndrome, in particular in the elderly (Gordon, 1998; Lantz *et al.*, 1999; Barbenel *et al.*, 2000; Beckman *et al.*, 2000; Parker *et al.*, 2001; Dannawi, 2002; Spinella and Eaton, 2002). This syndrome is characterized by confusion, agitation, hyperreflexia, shivering or tremor, diaphoresis, nausea, diarrhoea, lack of coordination, fever, coma, flushing or rhabdomyolysis (Cookson, 1993). A male patient receiving testosterone replacement postorchidectomy developed mania when taking St John's wort and sertraline together (Barbenel *et al.*, 2000); while a female patient with a history of mild traumatic brain injury and resultant depression experienced hypomania after adding St John's wort and *Ginkgo biloba* to her regimen of fluoxetine and buspirone, which remitted after discontinuation of the herbal medicines (Spinella and Eaton, 2002). Additive effect is considered to be the underlying mechanism. Hyperforin and other components from St John's wort have been shown to inhibit rat vesicular uptake of serotonin and dopamine (Wonnemann *et al.*, 2001; Roz *et al.*, 2002). Long-term treatment of rats with St John's wort and hypericin increased serotonin levels in rat hypothalamus and hippocampus (Butterweck *et al.*, 2002). Because the safety profile of combining SSRIs with St John's wort is not fully defined, the combined use of these two types of agents should be avoided.

Anticoagulants

Phenprocoumon In a single-blind, placebo-controlled crossover study, healthy volunteers ($n = 10$) taking St John's wort extract (LI 160) at 900-mg daily for 11 days before a single dose of phenprocoumon (an anticoagulant) had a lower AUC (by 17.4%) of the free fraction than when receiving the placebo only (Maurer *et al.*, 1999).

Warfarin The interaction between St John's wort and warfarin has been identified from spontaneous case reports (Ernst, 1999; Yue *et al.*, 2000). Seven cases of decreased warfarin effect following St John's wort treatment were reported to the Swedish Medical Products Agency (Yue *et al.*, 2000). From the years 1998–2000, 22 spontaneous cases of interactions with warfarin have been reported to regulatory authorities in Europe. These interactions all resulted in unstable international normalized ratio (INR) values, with a decrease in the INR value being the most commonly observed effect of St John's wort (Ernst, 1999; Yue *et al.*, 2000). Concomitant intake of St John's wort was associated with a loss of anticoagulant activity in patients stabilized on warfarin. Although no thromboembolic episodes occurred, the decrease in anticoagulant activity was considered clinically significant. Anticoagulant

activity was restored when St John's wort was terminated or the warfarin dose was increased.

These observations suggest an increased clearance of both warfarin and phenprocoumon, possibly due to the induction of CYPs, particular CYP2C9 and 3A4. Both warfarin and phenprocoumon are substrates of CYP2C9 (He *et al.*, 1999). Warfarin is also metabolized by CYP1A2 and 3A4 (Kaminsky and Zhang, 1997). Intake of St John's wort may induce CYP2C9 and 3A4, contributing to the loss of the anticoagulant activity.

Antihistamines

Fexofenadine Fexofenadine is a non-sedating antihistamine (Markham and Wagstaff, 1998) used as a probe substrate for P-gP (Cvetkovic *et al.*, 1999; Tian *et al.*, 2002). It does not undergo significant metabolic biotransformation because 95% of the dose is excreted unchanged either in the urine or faeces after biliary excretion (Lippert *et al.*, 1995). Fexofenadine is the active metabolite of the terfenadine, but has an advantage over the latter that it is not cardiotoxic and does not cause the rare but potentially fatal adverse reaction associated with certain drug interactions involving the latter (Woosley *et al.*, 1993).

In healthy subjects, a single dose of St John's wort (900 mg) significantly increased the C_{max} of fexofenadine by 45% and significantly decreased the oral clearance by 20%, with no change in the elimination half-life or renal clearance (Wang *et al.*, 2002). However, long-term administration of St John's wort (900 mg for 2 weeks) caused a 35% decrease in C_{max} of fexofenadine and a 47% increase in the oral clearance. In another clinical study in healthy subjects, treatment with St John's wort (900 mg/day) for 12 days also enhanced the oral clearance of fexofenadine by 1.6-fold (Dresser *et al.*, 2003). The differences in the extent of pharmacokinetic changes probably reflect the different study designs. It appears that a single dose of St John's wort caused significant inhibition of intestinal P-gP, whereas long-term treatment with the herb produced an opposing effect on P-gP and thus reversed the changes in fexofenadine disposition. An additional confounding factor is that the different preparations of St John's wort contain varying amounts of the active ingredients.

Anti-HIV agents

Protease inhibitors Some protease inhibitors have been found to interact with St John's wort. An open crossover study indicated that intake of St John's wort (900 mg/day, standardized to 0.3% hypericin) for 2 weeks led to a decrease in the plasma AUC of indinavir by 57% and the extrapolated 8-h indinavir trough concentration (C_{trough}) by 81% in eight healthy volunteers (Piscitelli *et al.*, 2000). Because indinavir is a CYP3A4 substrate (Chiba *et al.*, 1996), hepatic enzyme induction is thought to be the primary mechanism for the interaction. In addition, one spontaneous case has been reported in the UK, in which the patient experienced an increase in HIV RNA viral load following the use of St John's wort concomitantly with indinavir and lamivudine.

A reduced exposure to indinavir could lead to the development

of drug resistance and treatment failure in patients infected with HIV. Because many other protease inhibitors, such as amprenavir (Decker *et al.*, 1998) and saquinavir (Fitzsimmons and Collins, 1997), are also metabolized by the CYP3A4, they may be adversely influenced by concomitant intake of St John's wort. HIV patients being treated with protease inhibitors should avoid St John's wort. The European Medicine Evaluation Agency has recommended that patients receiving protease inhibitors such as indinavir for the treatment of HIV infection should not take St John's wort or other products containing this herb.

Reverse transcriptase inhibitor The ingestion of St John's wort elevated the oral clearance of the HIV reverse transcriptase inhibitor nevirapine (de Maat *et al.*, 2001). Nevirapine metabolism are catalysed by CYP2B6 and 3A4 (Erickson *et al.*, 1999).

Antitussive agents and bronchodilators

Dextromethorphan The antitussive drug dextromethorphan is routinely used as a probe substrate (Wieling *et al.*, 2000) to evaluate the activity of polymorphic CYP2D6 in humans (Bradford, 2002). In a clinical study to evaluate the effect of St John's wort intake on the orally administered drug, no interaction was evident when the drug was taken after exposure for 3 days to the herb, at a dose of 900 mg daily, and continued during the sampling period (Markowitz *et al.*, 2000). The herbal preparation did not alter the metabolic ratio in the urine (ratio of dextromethorphan to the metabolite dextrorphan).

Theophylline A case has been reported where a female patient required high doses of theophylline to attain therapeutic plasma levels (Nebel *et al.*, 1999). The use of a high dose of this drug became necessary when the patient started taking St John's wort (300 mg/day). When the ingestion of the herb was discontinued, theophylline plasma levels were doubled and the theophylline dose needed to be reduced. These observations suggest that the intake of St John's wort enhances the metabolism of theophylline. Theophylline is primarily metabolized by CYP1A2 (Sarkar *et al.*, 1992), implying that St John's wort induces the expression of this enzyme in the liver.

Hypoglycaemics

Tolbutamide Short- or long-term intake of St John's wort at 900 mg/day did not alter the AUC, oral clearance and $t_{1/2\beta}$ of the selective CYP2C9 substrate tolbutamide in healthy subjects (Wang *et al.*, 2001). However, an increased incidence of hypoglycaemia was observed when tolbutamide was coadministered with St John's wort. The unaltered total clearance of tolbutamide in the presence of St John's wort probably reflects the offsetting changes in intrinsic clearance and plasma protein binding of tolbutamide. However, this was excluded because the plasma protein binding of tolbutamide was unaffected by St John's wort (Wang *et al.*, 2001). It appears that the increased incidence of hypoglycaemia by St John's wort is due to a pharmacodynamic interaction.

Immunosuppressants

Cyclosporine Cyclosporine is a widely used immunosuppressive agent for transplantation with narrow therapeutic index (Akhlaghi and Trull, 2002), with allograft rejection occurring when its blood concentrations fall below the effective concentration (Akhlaghi and Trull, 2002). Cyclosporine is a substrate of PgP (Lown *et al.*, 1997) and CYP3A4 (Kronbach *et al.*, 1988; Combalbert *et al.*, 1989; Christians *et al.*, 1991; Jurima-Romet *et al.*, 1994). Therefore, induction of both CYP3A4 and PgP by St John's wort components may act to reduce the plasma level of cyclosporine to subtherapeutic levels, leading to clinically significant consequences such as the rejection of a transplanted organ. In healthy subjects, pretreatment of St John's Wort for 12 days increased the clearance of cyclosporine by approximately 1.9-fold (Dresser *et al.*, 2003).

A few case reports of interactions with cyclosporine by St John's wort have been published (Barone *et al.*, 2000; Karliova *et al.*, 2000; Mai *et al.*, 2000; Ruschitzka *et al.*, 2000). The published cases concerned include patients receiving transplantation of heart ($n = 2$), liver ($n = 1$), kidney ($n = 1$) and pancreas ($n = 1$). In all of these cases, a decreased blood trough concentration of cyclosporine was observed and was associated with transplant graft rejection. The decrease in cyclosporine levels ranged from 25% (Barone *et al.*, 2000) to 62% (Ruschitzka *et al.*, 2000) within 3–4 weeks of starting St John's wort. Some of the patients recovered spontaneously after stopping the herbal medicine, while others needed increased cyclosporine dose.

Thirty patients with kidney transplantation were found to have significantly decreased plasma cyclosporine concentrations by 47% (range 33–62%) (Breidenbach *et al.*, 2000b). This led to increased cyclosporine doses by 46% (range 15–115%). When the herbal remedy was withdrawn, cyclosporine concentrations were increased by 187% (range 84–292%) and the dose of cyclosporine was reduced to that taken before the intake of St John's wort. Another study involving 11 renal transplant patients indicated that treatment with St John's wort extract (600 mg/day) for 2 weeks decreased the AUC, C_{\max} and C_{trough} for cyclosporine by 41–46% (Bauer *et al.*, 2003). This was accompanied by substantially altered metabolite pattern of cyclosporine. Cyclosporine doses were increased by a median of 55.6% at day 15, with the first dose adjustment needed only 3 days after initiation of St John's wort treatment.

Tacrolimus and mycophenolic acid A recent case report associated St John's wort treatment with decreased tacrolimus concentrations in a renal transplant patient (Bolley *et al.*, 2002). More recently, the effect of St John's wort extract on the pharmacokinetics of the tacrolimus and mycophenolic acid in 10 stable renal transplant patients was demonstrated (Mai *et al.*, 2003). Treatment with St John's wort extract at 600 mg/day for 14 days reduced the AUC of tacrolimus by 57.8%, but the pharmacokinetics of mycophenolic acid remained unchanged. Tacrolimus dose adjustments from a median of 4.5 mg/day at baseline to 8.0 mg/day during treatment with St John's wort were required to maintain therapeutic tacrolimus concentrations. These findings demonstrate that

administration of St John's wort extract to patients receiving tacrolimus treatment may significantly decrease tacrolimus blood concentrations, leading to the risk of organ rejection. Because tacrolimus is extensively metabolized by CYP3A4 (Sattler *et al.*, 1992; Lampen *et al.*, 1995) and is a substrate of P-gP (Rao and Scarborough, 1994), induction of both CYP3A and P-gP by St John's wort is considered to be the main source of the interaction. The reason for the lack of interaction between mycophenolic acid and St John's wort is unclear. It may be due to the fact that mycophenolic acid is mainly metabolized by UGT1A8, 1A9, and 1A10, but not CYP3A (Mackenzie, 2000; Kelly and Kahan, 2002).

Cardiovascular drugs

Digoxin In a single-blind, placebo-controlled study involving 25 healthy subjects, no significant alteration of digoxin pharmacokinetics was observed following a single dose of St John's wort. However, repeated intake of the herb (LI160) at 900 mg/day for 10 days resulted in a decreased AUC (by 25%), C_{\max} (by 33%) and C_{trough} (by 26%), with the fall in concentration becoming more pronounced as the duration of St John's wort intake was increased (Johne *et al.*, 1999). It is considered that the altered pharmacokinetics of digoxin by the herbal remedy is due to induction of intestinal P-gP following multiple-dose treatment with St John's wort. Thus, the reduction in digoxin concentration observed is most likely due to altered absorption or distribution, rather than metabolism, as the elimination half-life ($t_{1/2\beta}$) for digoxin remained constant.

Digoxin is not significantly metabolized by CYPs in human hepatocytes and human liver microsomes (Lacarelle *et al.*, 1991). However, in contrast to human microsomes, microsomal CYP3A proteins have been shown to catalyse the sequential oxidative cleavage of digoxin in rat (Salphati and Benet, 1999). In a subsequent clinical study, the administration of St John's Wort extract to eight healthy male volunteers during 14 days resulted in an 18% decrease of digoxin exposure, and a 1.4-fold increased expression of duodenal P-gP after a single digoxin dose (0.5 mg) (Durr *et al.*, 2000). Digoxin is a well known substrate of P-gP (Schinkel *et al.*, 1995; Drescher *et al.*, 2003). Other inducers of digoxin clearance, such as rifampicin (Gault *et al.*, 1984; Greiner *et al.*, 1999) and phenytoin (Rameis, 1985), decrease digoxin plasma concentration mediated by P-gP. Flavonoids present in the St John's wort may contribute to the activation of P-gP (Conseil *et al.*, 1998). No spontaneous case reports of interactions between St John's wort and digoxin have been identified.

Simvastatin and pravastatin The effects of St John's Wort on the pharmacokinetics of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors simvastatin and pravastatin have been investigated in a double-blind, crossover study in healthy volunteers (Sugimoto *et al.*, 2001). Treatment of 16 healthy male subjects with St John's wort (900 mg/day) for 14 days decreased the C_{\max} by 28% and AUC by 52% of simvastatin hydroxy acid ($p < 0.05$), but not pravastatin. St John's wort also decreased the C_{\max} by 12% and AUC by 34% of simvastatin lactone, but the differences did not reach statistical significance ($p > 0.05$).

The interactions can be partly, if not completely, attributable to enhanced CYP3A4-mediated first-pass metabolism of simvastatin in the small intestine and liver by St John's wort. Simvastatin lactone is extensively metabolized by CYP3A4 in the intestine and liver (Vickers *et al.*, 1990; Prueksaritanont *et al.*, 1997), whereas the active form simvastatin hydroxyl acid is not a substrate for CYP3A4 and is metabolized by β -oxidation (Ubeaud *et al.*, 1999). Simvastatin lactone is a high clearance drug and its clearance is not sensitive to changes in hepatic enzyme activity. This may provide an explanation for the lack of effect of St John's wort on its elimination. In addition, lipophilic simvastatin lactone had a high affinity to P-gP, while the hydrophilic pravastatin did not inhibit P-gP-mediated transport (Bogman *et al.*, 2001), suggesting that simvastatin but not pravastatin is a substrate of P-gP. Therefore, an induction of P-gP by St John's wort may also partly contribute to the reduced AUC of simvastatin.

Opiates

Methadone Methadone is a phenylheptylamine opioid agonist used in the treatment of severe pain and opioid dependence (Krambeer *et al.*, 2001; Bruera and Sweeney, 2002). Long-term treatment with St John's wort (900 mg/day) for a median period of 31 days (14–47 days) lowered the C_{trough} of methadone by 47% in four patients (Eich-Hochli *et al.*, 2003). Two patients reported symptoms that suggested a withdrawal syndrome. The interaction may be due to induction of CYP3A4 that metabolizes methadone (Moody *et al.*, 1997). Thus, combination of St John's wort with methadone may induce withdrawal symptoms leading to resumption of illicit drug uses.

Loperamide Loperamide is a synthetic opioid agonist used as an antidiarrhoeal agent (Ooms *et al.*, 1984). This drug has become a standard treatment of irinotecan-induced diarrhoea in Europe and the USA (Abigeres and Armand, 1994; Hecht, 1998). The anti-secretory action of loperamide has been attributed to its agonistic effect on the opioid receptors, blockade of calcium channels and the calmodulin system in the colonic epithelium (Ruppel, 1987; Bleiberg and Cvitkovic, 1996). A case report exists describing a brief episode of acute delirium in a 39-year-old woman with depression and migraine when St John's wort was combined with loperamide and valerian (Khawaja *et al.*, 1999). The interaction outlined could be due to an additive effect resulting from monoamine oxidase inhibition by the herbal constituents from St John's wort. Loperamide has been reported to cause delirium (Schwartz and Rodriguez, 1991).

Oral contraceptives

The use of oral contraceptives is one of the most highly effective forms of contraception and provides many short- and long-term noncontraceptive health benefits (Borgelt-Hansen, 2001; Burkman *et al.*, 2001). Most steroids present in oral contraceptives are substrates of CYP3A4 (Thummel and Wilkinson, 1998). These hormones are also CYP inducers. St John's wort is a potent inducer of CYP3A4 (Moore *et al.*, 2000; Wang *et al.*, 2001; Dresser *et al.*,

Table 1 Reports on drug interactions with St John's wort

Drug	CYP(s) substrate	PgP substrate	Other concomitant drugs	Study type
Anticancer drug				
Irinotecan	3A4 (minor)	+	None	Open before-after comparison
Anticonvulsant				
Carbamazepine	3A4, 2C8	-	None	Open before-after comparison
Antidepressant				
Amitriptyline	2C19, 2D6, 3A4	-	None	Open before-after comparison
Sertraline	2B6, 2C9, 2C19, 2D6, 3A4	Unknown	1 PT: none; 1 PT: aspirin, vitamins; 1 PT: insulin	Case series
Sertraline	2B6, 2C9, 2C19, 2D6, 3A4	Unknown	Testosterone	Case report
Paroxetine	2D6	Unknown	None	Case report
Nefazodone	3A4	Unknown	None	Case report
Anticonvulsant				
Phenprocoumon	Unknown	Unknown	None	Single-blind, placebo-controlled, crossover
Warfarin	2C9	-	None	Case series
Antihistamine				
Fexofenadine	-	+	None	Open before-after comparison
Anti-HIV agents				
Indinavir	3A4	+	None	Before-after comparison
Nevirapine	2B6, 3A4	-	None	Case report
Antitussive agent and bronchodilator				
Dextromethorphan	2D6		None	Before-after comparison
Theophylline	1A2	-	Fruzemide, potassium, morphine, zolpidem, valproic acid, ibuprofen, amitriptyline, zafirlukast, triamcinolone, albuterol, prednisone	Case report
Cardiovascular drug				
Digoxin	-	+	None	Placebo-controlled parallel study
Simvastatin	3A4	+	None	Double-blind, crossover
Pravastatin	3A4	-	None	Double-blind, crossover
Hypoglycaemic				
Tolbutamide	2C9	-	None	Before-after comparison
Immunosuppressant				
Cyclosporine	3A4	+	None	Case report
Cyclosporine	3A4	+	None	Case report
Cyclosporine	3A4	+	Prednisone	Case report
Cyclosporine	3A4	+	Unreported drugs	Case series
Cyclosporine	3A4	+	None	Case series
Cyclosporine	3A4	+	None	Case series
Cyclosporine	3A4	+	Azathioprine, corticosteroids	Case report
Cyclosporine	3A4	+	Acetyldigoxin	Case report
Cyclosporine	3A4	+	Other immuno- suppressive agents	Case report
Cyclosporine	3A4	+	Mycophenolate or prednisone	Case report
Cyclosporine	3A4	+	None	Before-after comparison
Tacrolimus	3A4	+	None	Before-after comparison
Opiate				
Methadone	3A4, 2C8, 2D6	-	None	Case series
Loperamide	Unknown	Unknown	Valerian	Case report
Oral contraceptive	3A4	-	None	Case series
Oral contraceptive	3A4	-	None	Case series

Table 1 continued

Drug	CYP(s) substrate	PgP substrate	Other concomitant drugs	Study type
Sedative				
Alprazolam	3A4	–	None	Before-after comparison
Midazolam	3A4	–	None	Before-after comparison
Midazolam	3A4	–	None	Before-after comparison
Drug	Subjects	Outcomes involved	Possible mechanism of interaction	References
Anticancer drug Irinotecan	5 PTS	↓SN-38 by 42%, ↓myelosuppression	Modulation of PgP?	Mathijssen <i>et al.</i> (2002)
Anticonvulsant Carbamazepine	8 HV	↔AUC and oral CL of parent drug or carbamazepine -10,11-epoxide	?	Burstein <i>et al.</i> (2000)
Antidepressant Amitriptyline	12 PTS	↓AUC (amitriptyline) by 22% and nortriptyline by 41%	Induction of CYP3A	Johne <i>et al.</i> (2002)
Sertraline	4 PTS	Nausea, vomiting, anxiety, confusion, restlessness	Additive effect on serotonin uptake inhibition, enzyme inhibition?	Lantz <i>et al.</i> (1999)
Sertraline	1 PT	Manic episode	Additive effect on serotonin uptake inhibition, enzyme inhibition?	Barbenel <i>et al.</i> (2000)
Paroxetine	1 PT	Nausea, weakness, lethargy	Additive effect on serotonin uptake inhibition, enzyme inhibition?	Gordon (1998)
Nefazodone	1 PT	Nausea, vomiting, headache	Additive effect on serotonin uptake inhibition, enzyme inhibition?	Lantz <i>et al.</i> (1999)
Anticonvulsant Phenprocoumon	10 HV	↓AUC by 17.4%	Enzyme induction?	Maurer <i>et al.</i> (1999)
Warfarin	7 PTS	↓INR	Enzyme induction	Yue <i>et al.</i> (2000)
Antihistamine Fexofenadine	12 HV	↓C _{max} by 45% and oral CL by 20% (single dose of herb)	PgP inhibition	Wang <i>et al.</i> (2002)
Anti-HIV agents Indinavir	8 HV	↓AUC by 57%, C _{trough} by 81%	Enzyme induction	Piscitelli <i>et al.</i> (2000)
Nevirapine	PTS	↑CL	Induction of enzyme and PgP	de Maat <i>et al.</i> (2001)
Antitussive agent and bronchodilator Dextromethorphan	7 HV	↔dextromethorphan metabolic ratio		Markowitz <i>et al.</i> (2000)
Theophylline	1 PT	↓blood level	Enzyme induction	Nebel <i>et al.</i> (1999)
Cardiovascular drug Digoxin	25 HV	↓AUC by 25%, C _{max} by 33%, C _{trough} by 26%	PgP induction	Johne <i>et al.</i> (1999)
Simvastatin	16 HV	↓C _{max} and AUC of simvastatin hydroxy acid	Induction of enzyme and PgP	Sugimoto <i>et al.</i> (2001)
Pravastatin	16 HV	↔C _{max} and AUC		Sugimoto <i>et al.</i> (2001)
Hypoglycaemic Tolbutamide	12 HV	↔AUC, CL, C _{max} , V _d , t _{1/2β} , ↑hypoglycaemia episode	Additive effect?	Wang <i>et al.</i> (2001)
Immunosuppressant Cyclosporine	1 PT	↓blood concentration by 75%	Induction of enzyme and PgP	Rey and Walter (1998)

Cyclosporine	1 PT	↓ blood concentration, rejection reaction	Induction of enzyme and PgP	Bon <i>et al.</i> (1999)
Cyclosporine	1 PT	↓ blood concentration	Induction of enzyme and PgP	Bon <i>et al.</i> (1999)
Cyclosporine	30 PTS	↓ blood concentration by 47% (33–62%)	Induction of enzyme and PgP	Breidenbach <i>et al.</i> (2000b)
Cyclosporine	45 PTS	↓ blood concentration by 30–64%, rejection event in 1 PT	Induction of enzyme and PgP	Breidenbach <i>et al.</i> (2000a)
Cyclosporine	5 PTS	↓ blood concentration	Induction of enzyme and PgP	Roots <i>et al.</i> (2000)
Cyclosporine	1 PT	↓ blood concentration, rejection episode	Induction of enzyme and PgP	Ruschitzka <i>et al.</i> (2000)
Cyclosporine	1 PT	Rejection episode	Induction of enzyme and PgP	(Karlova <i>et al.</i> , 2000)
Cyclosporine	1 PT	↓ blood concentration, rejection episode	Induction of enzyme and PgP	Yue <i>et al.</i> (2000)
Cyclosporine	2 PTS	↓ blood concentration, rejection episode in 1 PT	Induction of enzyme and PgP	Barone <i>et al.</i> (2001)
Cyclosporine	11 PTS	↓ AUC by 46%, C_{max} by 42%, C_{trough} by 41%, altered metabolite profiles	Induction of enzyme and PgP	Bauer <i>et al.</i> (2003)
Tacrolimus	10 PTS	↓ AUC by 57.8%	Induction of enzyme and PgP	Mai <i>et al.</i> (2003)
Opiate				
Methadone	4 PTS	↓ C_{trough} by 47%	Enzyme induction	Eich-Hochli <i>et al.</i> (2003)
Loperamide	1 PT	Acute delirium episode	MAO inhibition	Khawaja <i>et al.</i> (1999)
Oral contraceptive	3 PTS	Intermenstrual bleeding	Enzyme induction	Bon <i>et al.</i> (1999)
Oral contraceptive	9 PTS	Intermenstrual bleeding	Enzyme induction	Yue <i>et al.</i> (2000)
Sedative				
Alprazolam	7 HV	↓ AUC by 41%, $t_{1/2}$ by 24%; ↑ C_{max} by 15% ($p > 0.05$)	Minor induction of CYP3A4	Markowitz <i>et al.</i> (2000)
Midazolam	12 HV	↑ oral CL by 108.9% and ↓ oral bioavailability by 39.3%; ↓ 20% of AUC (i.v.)	Induction of CYP3A4	Wang <i>et al.</i> (2001)
Midazolam	21 HV	↑ 1.5-fold (i.v.) and 2.7-fold (oral) of CL	Induction of CYP3A4	Dresser <i>et al.</i> (2003)

AUC, Total area under the plasma concentration-time curve; C_{max} , maximal plasma concentration; CL, clearance; HV, healthy volunteers; INR, international normalized ratio; PT(S), patient(s); $t_{1/2\beta}$, elimination half-life; TDM, therapeutic drug monitoring. ↑ = Increase; ↓ = Decrease; ↔ = Unchanged.

2003), thus raising the possibility of drug interactions with oral contraceptives (Murphy, 2002).

Breakthrough bleeding has been reported in women taking the oral contraceptive pill when concomitantly taking St John's wort (Ernst, 1999). This has also been attributed to increased CYP3A4-mediated metabolism of the steroids due to enzyme induction. It has already been observed that, in female patients with tuberculosis, the contraceptive pill may fail to offer the expected protection because rifampicin, a known CYP3A4 inducer, elevates the elimination of contraceptives (Bolt, 1994).

In several cases of unplanned pregnancies, intermenstrual bleeding mainly was experienced by young women taking oral contraceptives following ingestion of St John's wort for as little as 1 week (Yue *et al.*, 2000; Schwarz *et al.*, 2003). Discontinuation of the intake of St John's wort led to recovery by the women in those cases where the outcome was known. No blood concentrations have been measured and recorded in these case reports. A recent preliminary study found that administration of hypericum extract Ze 117 did not alter blood oestrogen concentrations

(Kaufeler *et al.*, 2001). Nevertheless, women using oral contraceptives should be warned against using St John's wort.

Sedatives

Alprazolam and midazolam A before–after comparison study indicated that 3-day ingestion of St John's wort extract (900 mg/day, SOLARAY®, standardized to 0.3% hypericin) insignificantly ($p .14$) decreased the AUC of alprazolam by 41% in healthy subjects ($n = 7$) (Markowitz *et al.*, 2000). In addition, there were no statistically significant changes in $t_{1/2}$ (decreased by 24%) and C_{max} (increased by 15%).

Similarly, short-term treatment with St John's wort extract at 900 mg/day did not significantly alter the pharmacokinetics of midazolam in healthy volunteers (Wang *et al.*, 2001). However, long-term administration of St John's wort (900 mg/day for 2 weeks) significantly increased the oral clearance of midazolam by 108.9% and decreased the oral bioavailability by 39.3% (Wang *et al.*, 2001). By contrast to a marked decrease (> 50%) in the

AUC of midazolam when administered orally, long-term St John's wort administration caused a relatively small decrease (20%) in AUC of midazolam when given intravenously (Wang *et al.*, 2001). Similarly, when St John's wort was administered for 12 days (Dresser *et al.*, 2003), the clearance of midazolam was significantly enhanced. In addition, treatment of St John's wort extract for 28 days gave a significant increase in the metabolism of midazolam when using the 1-hydroxymidazolam/midazolam serum ratios (1-h sample) as an indicator (Gurley *et al.*, 2002). Because alprazolam (von Moltke *et al.*, 1996) and midazolam (Gorski *et al.*, 1994) both are metabolized by CYP3A4, induction of hepatic enzyme (mainly CYP3A4) by St John's wort is considered to be the major mechanism for their altered pharmacokinetics.

Conclusions

Data from human studies and case reports indicate that St John's wort causes a number of drug interactions (Table 1). However, the induction of hepatic and intestinal CYP3A4 and/or P-gP may partly explain most of these. Because CYP3A4 is involved in the metabolism of more than 50% of all therapeutic drugs and P-gP mediates the intestinal and hepatic transport of many drugs, St John's wort is likely to interact with many more drugs than has been previously reported. Therefore, future development of St John's wort derivatives lacking activating property for pregnane X receptor and modulation of P-gP may enable its antidepressant activity and pharmacokinetic herb-drug interaction to be dissociated.

The clinical importance of drug interactions with St John's wort depends on a number of factors that are associated with coadministered drugs (dose, dosing regimen, administration route, pharmacokinetic and therapeutic range), herb (dose, dosing regimen and administration route) and patients (genetic polymorphism, age, gender and pathological conditions). Generally, a doubling or more in drug plasma concentration/AUC has the potential for enhanced adverse effects. However, less marked changes may still be clinically important for drugs with a steep concentration-response relationship or a narrow therapeutic index. In most cases, the extent of drug interactions with St John's wort varies markedly among individuals, depending on inter-individual differences in drug metabolizing enzymes (in particular CYP3A4) and transporters (e.g. P-gP), existing medical conditions, age and other factors. Because the potential interaction of St John's wort with other drugs is a major safety concern, particularly regarding drugs with narrow therapeutic indexes, additional systematic research on herb-drug interactions and appropriate regulation in safety, quality and efficacy of herbal medicines is needed.

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