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Review Article

Theme: Natural Products as Therapeutic Modulators
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Herb–Drug Interactions with St John's Wort (*Hypericum perforatum*): an Update on Clinical Observations

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Abstract. St John's wort (SJW) extracts, prepared from the aerial parts of *Hypericum perforatum*, contain numerous pharmacologically active ingredients, including naphthodianthrones (e.g., hypericin and its derivatives), phloroglucinols derivatives (e.g., hyperforin, which inhibits the reuptake of a number of neurotransmitters, including serotonin), and flavonoids. Such extracts are widely used for the treatment of mild-to-moderate depression. As a monotherapy, SJW has an encouraging safety profile. However, relevant and, in some case, life-threatening interactions have been reported, particularly with drugs which are substrate of cytochrome P450 and/or P-glycoprotein. Well-documented SJW interactions include (1) reduced blood cyclosporin concentration, as suggested by multiple case reports as well as by clinical trials, (2) serotonin syndrome or lethargy when SJW was given with serotonin reuptake inhibitors, (3) unwanted pregnancies in women while using oral contraceptives and SJW, and (4) reduced plasma drug concentration of antiretroviral (e.g., indinavir, nevirapine) and anticancer (i.e., irinotecan, imatinib) drugs. Hyperforin, which is believed to contribute to the antidepressant action of St John's wort, is also strongly suspected to be responsible of most of the described interactions.

KEY WORDS: cytochrome P450 enzymes; herb–drug interactions; herbal products; P-glycoprotein; St John's wort.

INTRODUCTION

A growing percentage of the population is using herbal products for preventive and therapeutic purposes. Herbal product annual retail sales reflect the growing consumer interest; indeed, sale statistics demonstrate a 3.4% increase from 2003 to 2004 and an additional 2.1% increase in 2005 compared to 2004 for all herbal products (1). The reason of this wide usage of natural drugs is the notion that, being natural, all herbs are safe. However, contrary to popular belief that "natural is safe", herbal drugs can cause significant side effects, including herb–drug interactions (2–4). In the last years, concerns about interactions between the natural top-selling antidepressant remedy *Hypericum perforatum* and conventional drugs have been raised (5–8). *H. perforatum*, more commonly known as St John's wort (SJW), is a herbaceous perennial plant native to Europe. Extracts obtained from the aerial parts of *H. perforatum* have been recommended traditionally for a wide range of medical conditions. The most common modern-day use of St John's wort commercial extracts (Table I) is for the treatment of depression. Several systematic reviews report St John's wort to be more effective than placebo and equally effective as synthetic antidepressant drugs in the short-term treatment of depressive disorders, including major depression (9–11). Experimentally, SJW and its active ingredient hyperforin have been shown to inhibit the reuptake of several neurotransmitters such as serotonin, noradrenaline, dopamine, glutamate, and gamma-aminobutyric acid (12,13).

Given the widespread use of SJW and in light of the consideration that herb–drug interaction is an important safety concern, we provide here an overview of the clinical data regarding the interaction between this herbal remedy and prescribed drugs. Reviews on St John's wort–drug interactions can be found elsewhere (6,14).

INFLUENCE OF ST JOHN'S WORT ON CYTOCHROME P450 ENZYMES AND P-GLYCOPROTEIN

Cytochrome P450 (CYP) enzymes are common sites of drug interactions in human. Drugs may act as inhibitors or inducers of CYPs, leading to altered clearance of a second drug (15). Strong evidence from animal studies as well as preclinical and clinical studies suggests that SJW may modulate CYP activity. Using well-established probe drugs (e.g., alprazolam and midazolam for CYP3A4, caffeine for CYP1A2, chlorzoxazone for CYP2E1, dextromethorphan and debrisoquine for CYP2D6, tolbutamide for CYP2C9, and omeprazole for CYP2C19), a number of clinical trials

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Table I. Some Commercially Available St John's Wort Extracts Evaluated for Possible Drug Interactions

Extract type or brand name	Standardization	Pharmaceutical form	Manufacturer
Esbericum®	Hyperforin 1.47%	Capsules containing 60 mg of SJW extract	Schaper & Bruemmer, Salzgitter, Germany
Hypericum 2000 plus®	Hypericin 0.055%, hyperforin 0.75%	Capsules containing SJW extract (equivalent to 2 g dry herb), *Ginkgo biloba* (equivalent to leaf dry 100 mg), and nutritional cofactors	Nutra-Life, New Zealand
Jarsin 300®	Hypericin 0.28%	Tablets containing 300 mg of SJW dried extract (LI-160™)	Lichtwer Pharma AG, Berlin, Germany
Kira® (USA)			
Kira® (UK)	Hypericin 0.28%	Tablets containing 100 mg of SJW dried extract (LI-160™)	Lichtwer Pharma AG, Berlin, Germany
LI-160	Hypericin 0.12–0.28%	Dried extract of SJW flowers and leaves	Lichtwer Pharma AG, Berlin, Germany
Neuroplant®	Hypericin 0.12–0.28%, hyperforin 3–6%	Tablets containing 300 mg (Neuroplant®) or 600 mg (Neuroplant® AKTIV) WS® 5570 dried extract	Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany
Neuroplant® AKTIV			
Movina®	Hyperforin 3–6%	Capsules containing 300 mg of SJW extract	Boehringer Ingelheim AB, Skärholmen, Sweden
Solaray®	Hypericin 0.12–0.3%	Capsules containing 300 mg SJW extract	Solaray
TruNature®	Hypericin 0.3%	Soft gels containing 300 mg SJW extract	Leiner Health Products, Carson, CA, USA
WS® 5570	Hypericin 0.12–0.28%, hyperforin 3–6%	Dried extract of SJW flowers and leaves	Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany
Ze 117	Hypericin 0.2% and low content of hyperforin (<0.5%)	50% (*w/w*) ethanol extract of SJW	Zeller AG, Switzerland

SJW St John's wort

have consistently shown that SJW induces CYP3A4, CYP2E1, and CYP2C19, with no effect on CYP1A2, CYP2D6, or CYP2C9 (16–30). Some authors have also suggested that SJW may induce CYP1A2 only in females (24). The effect of St John's wort on CYP3A4 has been investigated more in detail. The effect of SJW on midazolam pharmacokinetics was considerably less evident after intravenous administration than after oral administration (22,25). These results suggest that the primary site of action of SJW is the intestinal—rather than hepatic—CYP3A4. Also, Imai and colleagues found that the *in vivo* CYP3A4 activity returned progressively to the basal level approximately 1 week after cessation of SJW, with an estimated half-life of 46.2 h (29). Hyperforin is the chemical ingredient of SJW-induced interactions. Indeed, this phloroglucinol derivative has been demonstrated to be a potent ligand for the nuclear receptor that regulates the expression of CYP3A4 (31).

P-glycoprotein, one of the most clinically important transmembrane transporters in humans, is encoded by the ABCB1/MDR1 gene. P-glycoprotein is located on the apical surface of intestinal epithelial cells, bile canaliculi, renal tubular cells, and placenta and the luminal surface of capillary endothelial cells in the brain and testes. The specific localization of P-glycoprotein suggests an active role in drug elimination and absorption (32). SJW has been shown to induce P-glycoprotein expression in intestinal isolated cells (33) as well as in the human intestine in healthy volunteers (34). Accordingly, SJW has been shown to lower plasma concentration of well-known P-glycoprotein substrates, including digoxin (35–37), fexofenadine (25,27), and talinolol (38). The effect on probe substrates was associated to increased MDR1 mRNA as well as P-glycoprotein levels in the human intestinal mucosa (38).

The effect of SJW on P-glycoprotein or CYP enzymes is generally observed after long treatment [ten or more days (25,27,35,39); data with treatment for lesser numbers of days (i.e., 4–9 days) are not available] with studies reporting no effect (or even nonclinically relevant stimulating effects) following acute (1–3 days) SJW administration (19,40). Effects on CYP or P-glycoprotein after SJW treatment in the 4–9-day range are not available. In addition, the extent of CYP3A4 and P-glycoprotein induction was found to be comparable among a number of ethnic groups, namely Caucasians, Africans, Americans, Hispanics, Chinese, Indians, and Malays (27).

The relative importance of hyperforin, one of the active ingredient of St John's wort, on CYP and P-glycoprotein expression has been evaluated also in clinical trials (21,41–45). Hyperforin is a potent inducer of CYP3A4 and P-glycoprotein (46). Clinical results suggest that the hyperforin content determines the magnitude of St John's wort interactions, since extracts with low hyperforin content had a weak or no effect on both CYP and P-glycoprotein probe drugs (21,41–45). Thus, clinical trials have reported that St John's wort extracts with low hyperforin content did not change the pharmacokinetic of alprazolam and midazolam (CYP3 substrate) (21,43), tolbutamide (CYP2C9 substrate) (21), digoxin (P-glycoprotein substrate) (21), cyclosporine (metabolized by CYP3A4 and effluxed by P-glycoprotein) (41), ethinylestradiol, and desogestrel, components of oral contraceptive pills (45).

CONVENTIONAL DRUGS AFFECTED BY ST JOHN'S WORT

SJW has been shown to clinically interact with a number of drugs (Tables II and III), including immunosuppressants, contraceptives, cardiovascular, anti-HIV and anticancer drugs, anxiolytics, antidepressants, anticonvulsants, anesthetics, drugs used in addicted patients (e.g., methadone), muscle relaxing agents, drugs acting on the respiratory system, hypoglycemic, antimicrobic, and antimigraine medicines as well as drugs acting on the gastrointestinal tract. These interactions are discussed below.

Immunosuppressants

The importance of unrecognized interactions between SJW and immunosuppressants is particularly relevant in transplant recipients as serious consequences have occurred. The interaction between SJW and cyclosporine is the most well documented among herb–drug interactions, as it has been highlighted by multiple case reports, case series (47–61), and clinical trials (25,41). A number of heart, renal, or liver transplant patients stabilized on cyclosporine showed decreased blood levels (associated, in some cases, with acute rejection episodes) after taking SJW at therapeutic dosage. The clinical picture improved in all cases following discontinuation of the herbal extract (60). Cyclosporine is a substrate of P-glycoprotein, and it is also metabolized by CYP3A4.

Tacrolimus is an immunosuppressive drug frequently used after renal transplantation. Low tacrolimus blood levels may result in rejection episodes with the risk of graft loss, whereas high tacrolimus levels may be associated with nephrotoxicity. Therefore, drug interactions with tacrolimus are of special interest. A 65-year-old renal transplant patient showed its plasma tacrolimus levels to be sharply decreased after 1 month self-treatment with SJW extract. Tacrolimus levels returned to the previous range of concentrations after stopping SJW assumption (62). This clinical case has been confirmed by two trials showing decreased tacrolimus area under the curve (AUC) both in healthy volunteers (63) and in renal transplant patients (64). In the latter study (64), dose increases were required to maintain therapeutic tacrolimus concentrations. Notably, SJW was found to decrease the blood concentrations of tacrolimus (a CYP3A4 and P-glycoprotein substrate), but not of mycophenolic acid (mainly glucuronidated by UGT1A9 and 2B7) (64).

Prednisone is a well-known glucocorticoid that has been relied upon in the treatment of immune-exacerbated conditions. A case of mania due to coadministration of SJW and prednisone has been reported (65). Both SJW and prednisone may cause mania when administered alone. In this case, causality needs to be established since the patient was a cocaine and alcohol abuser. Notably, SJW had no effect on prednisone pharmacokinetics in healthy volunteers (66).

Hormonal Therapy

Several cases of intermenstrual bleeding have been reported in young woman on oral contraceptives after taking SJW for as little as 1 week (46,67). This adverse event has been observed also in clinical studies (28,68,69) that have shown a higher incidence of intracyclic bleeding episodes after coadministration of SJW and oral contraceptive pills. Most importantly, reports of women becoming pregnant while using oral contraceptives and SJW have been reported by UK, German, and Swedish authorities. Furthermore, a detailed clinical case of unwanted pregnancy in a depressed 36-year-old woman has been reported (70). The patient began self-medication with St John's wort for approximately 3 months prior to conception, and until conception, no other medication was taken except the hormonal contraceptive (ethinylestradiol/dienogesterol).

Both intermenstrual bleeding and reduced efficacy are believed to be due to the reduced plasma concentration of the components of oral contraceptive pills by SJW. It is well known that drugs inducing CYP3A4 such as rifampicin may cause reduced efficacy of oral contraceptives and breakthrough bleeding (71). Clinical studies have shown that SJW increases the clearance of oral pill components such as ethinylestradiol, norethindrone, and ketodesogestrel, and this effect is associated to breakthrough bleeding (28,68,69); interestingly, SJW extracts with low hyperforin content were found not to alter the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel, the hormonal components of the oral contraceptive (45). This further highlights the concept that hyperforin is the chemical ingredient responsible of SJW-induced pharmacokinetic interactions.

Tibolone, an analog of the progestin, norethynodrel, influences the synthesis and metabolism of endogenous estrogen, progesterone, and androgen. Tibolone is used for the treatment of menopausal symptoms and for the postponement and calming of symptoms accompanying age-related diseases (72). A case of a patient under tibolone therapy for 2 years who developed a mixed-type liver injury with prolonged cholestasis and features of the vanishing bile duct syndrome following a 10-week treatment with SJW has been reported (73). In the absence of evidence of a potential role for concomitant medication, an interaction between the herbal preparation and tibolone was suspected as the likely cause of liver damage

Anticoagulants

The anticoagulant warfarin has a narrow therapeutic index and represents the most investigated drug with respect to drug interactions (74). The anticoagulant exists as a racemic mixture of R- and S-enantiomers, with R-warfarin being metabolized mainly by CYP1A2 and CYP3A4 and S-warfarin, which is more potent, predominantly by CYP2C19A (75). A clinical trial preformed in 12 healthy male subjects showed that SJW significantly induced the apparent clearance of both S-warfarin and R-warfarin, which, in turn, resulted in a significant reduction in the pharmacological effect of racemic warfarin (76). Similarly, another trial found that SJW decreased plasma levels of phenprocoumon (a coumarin anticoagulant chemically related to warfarin) (77). These clinical trials would explain the cases of decreased international normalized ratio observed following coadministration of SJW with warfarin (67) or phenprocoumon (47).

Table II. Case Reports and Case Series Reporting Interactions Between St John's Wort and Prescribed Drugs

Prescribed drug (reference)	SJW extract, dosage/duration	Sex (M/F)/age (years)	Clinical result of interaction	Possible mechanism	Comment
Adrenergic vasopressors (ephedrine 50 mg and phenylephrine 1 mg, bolus) (107)	NR, 6 months	F/23	Decreased responsiveness to vasopressors	Unknown (SJW might theoretically reduce the expression of adrenergic receptors)	The possibility that the anesthetic alone may have caused hypotension cannot be ruled out
Anesthetics (fentanyl, propofol, sevoflurane in O_2, and N_2O) (110)	Extract standardized to 0.3% hypericin, 500–1,000 mg tid for 3 months	F/21	Delayed emergence	Unknown	The American Society of Anesthesiologists advises that the use of SJW should be discontinued 2 or 3 weeks before surgery
Bupropion (110)	NR, 300 mg once a day for several years	F/58	Persistent orofacial dystonia	Additive effect on 5-HT reuptake	It is not recommended to use SJW in combination with 5-HT reuptake inhibitors or 5-HT ligands
Buspirone and fluoxetine (96)	NR	F/42	Hypomanic episode, with prominent anxious features and underlying depression	Additive effect on 5-HT signaling	The cases were complicated by the concomitant use of fluoxetine (one case) or *Ginkgo biloba* (both cases)
Buspirone (95)	Hypericum 2000 plus®—3 capsules daily for 2 months	F/27	Serotonin syndrome	Additive effect on 5-HT signaling	
Cyclosporine (47)	NR, 300 mg bid	F/61	Lowering of blood cyclosporine levels; rejection episode	Induction of CYP3A4 and/or P-glycoprotein	Physicians should be aware of this interaction (which causes acute rejection episode) when treating patients with cyclosporine
Cyclosporine (47)	NR, 300 mg tid	F/54	Lowering of blood cyclosporine levels	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (48)	NR	30 patients, NR	Lowering of blood cyclosporine levels (47%)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (49)	NR	10 patients, NR	Lowering of blood cyclosporine levels (49%); rejection episode in 1 patient	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (50)	Extract, 300 to 900 mg daily Tea: NR	5 patients, NR	Lowering of blood cyclosporine levels	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (51)	NR	F/mid-20s	Lowering of blood cyclosporine levels (75%)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (52)	LI 160, 300 mg tid for 3 weeks	NR/61	Lowering of plasma cyclosporine levels to 95 g/L; rejection episodes	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (52)	LI 160, 300 mg tid for 3 weeks	NR/63	Lowering of blood cyclosporine levels to 87 g/L; rejection episode	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (53)	Extract standardized to 0.3% hypericin, 300–600 mg/daily for 2 months	F/29	Lowering of blood cyclosporine (from 250–300 to 155 ng/mL): moderate to severe refection episode	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (54)	Jarsin® 300 mg/daily for 4 weeks	F/55	Lowering of blood cyclosporine, (from 131 to 74 ng/mL)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (55)	NR, 2× 900 mg/day for 2 weeks	M/63	Lowering of blood cyclosporine levels; rejection episode	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (56)	NR, for 3 days	F/38	Lowering of blood cyclosporine (from 147 to 39.7 ng/mL)	Induction of CYP3A4 and/or P-glycoprotein	

Cyclosporine (57)	Extract standardized to 0.3% hypericin F/44, 600–900 mg/daily for 6 months M/29, 300–600 mg/daily for 30 days	F/44 and M/29	Lowering of blood cyclosporine; acute rejection episode in M/29	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (58)	NR, for 2–5 weeks	3 patients, NR	Lowering of blood cyclosporine (<100 ng/mL)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (59)	Neuroplant®, 300 mg tid for 5 years	F/55	Lowering of blood cyclosporine (81 ng/mL)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (60)	NR, 300 mg bid for 26 days	M/58	Lowering of blood cyclosporine levels (from 200 to 67 μg/L)	Induction of CYP3A4 and/or P-glycoprotein	
Cyclosporine (61)	Herbal tea mixture containing SJW, NR	M/57	Lowering of blood cyclosporine levels (from from 100–130 to 70 μg/L)	Induction of CYP3A4 and/or P-glycoprotein	
Eletriptan (119)	NR, for 1 month	F/28	Serotonin syndrome	Additive effect on 5-HT signaling	The patient also took fluoxetine, which probably predisposed the patient to develop the syndrome precipitated by subsequent use of eletriptan
Loperamide (122)	NR	F/39	Brief episode of acute delirium (disoriented, agitated, confused state)	Unknown	If confirmed, such interaction is potentially dangerous
Nefazodone (97)	NR, 300 mg tid for 3 days	F/84	Nausea, vomiting, headache	Additive effect on 5-HT reuptake	The syndrome could be fatal particularly in the elderly
Nevirapine (87)	NR, for several months	5 M/range from 34 to 53	Decreased plasma concentration of nevirapine	Induction of CYP (CYP3A4)	SJW may render ineffective nevirapine treatment
Oral contraceptive (67)	NR	F/NR	Changed menstrual bleeding	Induction of CYP3A4	Physicians should be aware of this interaction. Changes in the pharmacokinetic of oral contraceptive pills can result in reduced efficacy and increased breakthrough bleeding
Oral contraceptive (67)	NR	8 F/range from 23 to 31	Intermenstrual bleeding	Induction of CYP3A4	
OC: ethinylestradiol desogestrel (47)	NR	F/NR	Intermenstrual (breakthrough) bleeding	Induction of CYP3A4	
OC: ethinylestradiol desogestrel (47)	NR	F/NR	Intermenstrual (breakthrough) bleeding	Induction of CYP3A4	
OC: ethinylestradiol desogestrel (47)	NR	F/44	Intermenstrual (breakthrough) bleeding	Induction of CYP3A4	
OC, Valette® (70)	NR, 1,700 mg daily for 3 months	F/36	Unwanted pregnancy	Induction of CYP3A4	
Paroxetine (98)	NR, 600 mg/day for 10 days	F/50	Nausea, weakness, fatigue, groggy, and lethargic state	Additive effect on 5-HT reuptake	The syndrome could be fatal particularly in the elderly
Phenprocoumon (47)	NR	F/75	Increased "Quick-Wert test" (indicating decreased anticoagulant effect)	Induction of CYP3A4 and possibly other CYP isoforms	The decreased plasma levels of phenprocoumon could be clinically relevant
Prednisone (65)	NR	F/36	Maniac episode	Unknown	A clinical trial did not confirm this interaction (66)
Sertraline (97)	NR	F/78	Dizziness, nausea, vomiting, headache	Additive effect on 5-HT reuptake	The syndrome could be fatal particularly in the elderly
Sertraline (97)	NR	M/64	Nausea, epigastric pain, anxiety	Additive effect on 5-HT reuptake	

Table II. (continued)

Prescribed drug (reference)	SJW extract, dosage/duration	Sex (M/F)/age (years)	Clinical result of interaction	Possible mechanism	Comment
Sertraline (97)	NR, 300 mg bid for 2 days	M/82	Nausea, vomiting, anxiety, confusion	Additive effect on 5-HT reuptake	
Sertraline (97)	NR, 300 mg tid for 2 days	M/79	Nausea, anxiety, feelings of restlessness, and irritability	Additive effect on 5-HT reuptake	
Sertraline (100)	Dosage unclear: for 5 weeks	M/28	Manic episode	Additive effect on 5-HT reuptake	
Tacrolimus (62)	Neuroplant®—600 mg/daily for 1 month	M/65	Decreased tacrolimus levels	Induction of CYP3A4	Physicians should be aware of this interaction (which causes acute rejection episode)
Theophylline (114)	Extract standardized to 0.3% hypericin, 300 mg/daily for 2 months	F/42	Decreased theophylline levels	Induction of CYP2E1 and CY3A4	A clinical trial did not confirm this interaction (115)
Tibolone (73)	NR: infusion 2 g/daily for 10 weeks	F/57	Acute hepatitis	Unknown	In absence of evidence of a potential role for concomitant medication, an interaction between SJW and tibolone was suspected as likely case of liver damage
Tryptophan (112)	NR	M/19	Serotonin syndrome (agitation, anxiety, tremors)	Additive effects (tryptophan may increase central serotonin levels)	The case was complicated by the use of an unknown antitussive drug
Venlafaxine (99)	Tincture, 200 gtt tid; usual dose 160 daily	M/32	Serotonin syndrome	Additive effect on 5-HT reuptake	The syndrome could be fatal particularly in the elderly
Warfarin (67)	NR	F/79	Decreased INR (from 2.5–3.8 to 1.7)	Induction of CYP3A4 and possibly other CYP isoforms	The decreased plasma levels of warfarin could be clinically relevant
Warfarin (67)	NR	M/65	Decreased INR (from 2.4–3.6 to 2.0–2.1)	Induction of CYP3A4 and possibly other CYP isoforms	
Warfarin (67)	NR	M/76	Decreased INR (from 2.6 to 1.1)	Induction of CYP3A4 and possibly other CYP isoforms	
Warfarin (67)	NR	F/61	Decreased INR (INR before treatment not available; INR after 1.2)	Induction of CYP3A4 and possibly other CYP isoforms	
Warfarin (67)	NR	F/84y	Decreased INR (from 2.9–3.6 to 1.5)	Induction of CYP3A4 and possibly other CYP isoforms	
Warfarin (67)	NR	F/56	Decreased INR (from 2.6 to 1.5)	Induction of CYP3A4 and possibly other CYP isoforms	
Warfarin (67)	NR	F/85	Decreased INR (from 2.1–4.1 to 1.5)	Induction of CYP3A4 and possibly other CYP isoforms	

NR not reported, *bid* twice daily, *CYP* cytochrome, *INR* international normalized ratio, *tid* three times daily, *OC* oral contraceptive, *SJW* St John's wort, *5-HT* 5-hydroxytryptamine

Table III. Clinical Trials Reporting Interactions Between St John's Wort and Prescribed Drugs

Prescribed drug (reference)	SJW extract, dosage/duration	Sample size	Clinical result of interaction	Possible mechanism	Comments
Alprazolam (19)	Solaray®, 300 mg tid for 3 days	4 males 3 females	No significant effect on plasma alprazolam (T_{max}, C_{max}, and AUC)	No effect on CYP3A4 after 3 days SJW	The interaction occurs only at therapeutic dose of SJW (300 mg tid for at least 10 days)
Alprazolam (20)	Kira®, 300 mg tid for 14 days	6 males 6 females	Decreased alprazolam AUC and half-life	Induction of CYP3A4	
Alprazolam (21)	Esbericum®, 1 capsule (60 mg extract) bid for 10 days	18 males 10 females	Marginal influence of alprazolam pharmacokinetics	Weak or no induction of CYP3A with a SJW extract with low hyperforin content	
Amitriptyline (102)	LI160, Jarsin®, 300 mg tid for 14 days	3 males 9 females	Decreased amitriptyline AUC	Induction of CYP3A4 and/or induction of P-glycoprotein	Physicians should be aware of this interaction when treating patients with amitriptyline
Atorvastatin (79)	Movina®, 300 mg bid for 4 weeks	10 males 6 females All hypercholesterolemic	Reduced efficacy of atorvastatin	Induction of CYP3A4 and/or induction of P-glycoprotein	SJW should not be given concomitantly to statins which are cytochrome P-450 or P-glycoprotein substrates
Carbamazepine (103)	Extract standardized to 0.3% hypericin, 300 mg tid for 14 days	5 males 3 females	No changes in carbamazepine pharmacokinetics	None	Carbamazepine is also metabolized by other CYP isoforms, such as CYP2C8. This may explain the lack of interaction
Caffeine (22)	Extract standardized to 0.3% hypericin, 900 mg single dose or 300 mg tid for 14 days	7 males 5 females	No effect on caffeine pharmacokinetics	No effect on CYP1A2	Clinical trials consistently show that SJW has a weak or no effect on caffeine pharmacokinetics
Caffeine (21)	Esbericum®, 1 capsule (60 mg extract) bid for 10 days	18 males 10 females	Marginal influence of caffeine pharmacokinetics	Weak or no induction of CYP1A2 with a SJW extract with low hyperforin content	
Caffeine (23)	Extract standardized to 0.3% hypericin and 4% hyperforin, 300 mg tid for 14 days	12 males	No effect on caffeine metabolism	No effect on CYP1A2	
Caffeine (24)	Jarsin®, 300 mg tid for 14 days	8 males 8 females	Increased caffeine metabolic ratios in saliva (only in females)	CYP1A2 induction in female only	
Caffeine (18)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	Increased (26%) paraxanthine/caffeine serum ratios	Weak induction of CYP1A2	
Caffeine (17)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	No changes in paraxanthine/caffeine serum ratios	No effect on CYP1A2	
Chlorzoxazone (18)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	Strong increase (110%) in hydroxychlorzoxazone/ chlorzoxazone ratio	Strong induction of CYP2E1	The therapeutic manifestation of such interaction has been not determined
Chlorzoxazone (17)	Extract standardized to hypericin 0.3%, 300 mg tid for 28 days	6 males 6 females	Increased hydroxychlorzoxazone/ chlorzoxazone serum ratios	Induction of CYP2E1	

Table III. (continued)

Prescribed drug (reference)	SJW extract, dosage/duration	Sample size	Clinical result of interaction	Possible mechanism	Comments
Cyclosporine (25)	LI160, 300 mg tid for 12 days	10 males 10 females	Increased cyclosporine clearance	Induction of CYP3A4 and/or P-glycoprotein	Physicians should be aware of this interaction when treating patients with cyclosporine
Cyclosporine (41)	300 mg tid for 14 days. Two preparation were used: low (0.1 mg/capsule) and high (7.0 mg/capsule) hyperforin content	9 males 1 female All renal transplant patients	Decreased AUC. Effect more pronounced for the high hyperforin content extract	Induction of CYP3A4 and/or P-glycoprotein	
Debrisoquine (18)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	Increased (23%) debrisoquine urinary recovery ratios;	Weak induction of CYP2D6	SJW does not affect the pharmacokinetics of CYP2D6 substrates
Debrisoquine (17)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	No changes in debrisoquine urinary recovery ratios	No effect on CYP2D6	
Debrisoquine (16)	Extract standardized to 3% hyperforin, 300 mg tid 14 days	8 males 8 females	No effect on debrisoquine urinary recovery ratios	Not applicable (no effect on CYP2D6)	
Dextromethorphan (19)	Solaray®, 300 mg tid for 3 days	4 males 3 females	No effect on dextromethorphan pharmacokinetics	No effect on CYP3A4 after 3-days SJW	SJW does not affect the pharmacokinetics of CYP2D6 substrates
Dextromethorphan (22)	Extract standardized to 0.3% hypericin, 900 mg single dose or 300 mg tid for 14 days	8 males 5 females	No effect on dextromethorphan pharmacokinetics	No effect on CYP2D6	
Dextromethorphan (26)	Extract standardized to 3% hyperforin, 300 mg tid for 14 days	4 males 9 females	No significant changes in dextromethorphan–dextrorphan ratio	No effect on CYP2D6	
Dextromethorphan (20)	Kira®, 300 mg tid for 14 days	6 males 6 females	No significant changes in dextromethorphan excretion	No effect on CYP 2D6	
Dextromethorphan (24)	Jarsin®, 300 mg tid for 14 days	8 males 8 females	No changes in dextromethorphan urinary excretion	No effect on CYP2D6	
Digoxin (35)	LI 160, 300 mg tid for 10 days	13 males 12 females	Decreased plasma digoxin concentration–trough concentration (33.3%), AUC (25%), and C_{max} (26%)	Induction of P-glycoprotein	Physicians should be aware of this interaction when treating patients with digoxin
Digoxin (36)	Various preparations, including powder, tea, juice, and extract LI160 for 14 days	96 healthy volunteers	Decreased plasma digoxin concentration (AUC, C_{max}, C_{trough})	Induction of P-glycoprotein	
Digoxin (21)	Esbericum®, 1 capsule (60 mg extract) bid for 10 days	15 males 13 females	Marginal influence on digoxin pharmacokinetics	Weak or no effect on P-glycoprotein with an extract with low hyperforin content	
Digoxin (16)	SJW (extract standardized to 3% hyperforin) 300 mg tid for 14 days	9 males 9 females	Significant reductions in AUC_{0-3} (28%), AUC_{10-24} (23%), and C_{max} (36%)	Induction of P-glycoprotein	

Digoxin (37)	LI160, 300 mg tid for 14 days	8 males	Decreased (18%) digoxin AUC	Induction of P-glycoprotein	
Erythromycin (37)	LI160, 300 mg tid for 14 days	8 males	Increased metabolism of erythromycin (as revealed by ^{14}C-erythromycin breath test)	Induction of CYP3A4	The clinical manifestation of such interaction remain to be determined
Fexofenadine (39)	SJW (extract standardized to hypericin 0.3%) single dose 900 mg or 300 mg tid for 14 days	9 males 3 females	Increased fexofenadine maximum plasma concentration after 1-day St John's administration. No effect after 14 days	Transient inhibition of P-glycoprotein after 1-day SJW administration	The transient inhibition of P-glycoprotein is clinically irrelevant
Fexofenadine (25)	LI160, 300 mg tid for 12 days	10 males 10 females	Increased fexofenadine clearance	Induction of P-glycoprotein	
Fexofenadine (27)	SJW (unspecified extract) 300 mg tid for 10 days	20 males 8 females	Decreased plasma concentration of fexofenadine	Induction of P-glycoprotein	
Gliclazide (116)	LI160, 300 mg tid for 15 days	15 males 6 females	Decreased gliclazide $AUC_{0-\infty}$, $t_{1/2}$, and apparent clearance	The mechanism seems independent of CYP2C9 genotype	The therapeutic manifestation of such interaction was not determined
Imatinib (91)	LI160, 300 mg tid for 14 d	6 males 6 females	Decreased imatinib AUC, $t_{1/2}$, and C_{max}	Induction of CYP3A4	Clinicians should be aware that SJW may reduce imatinib exposure by 30–40% and should take appropriate action to educate patients receiving imatinib
Imatinib (92)	SJW (HBC Inc, Los Angeles) 300 mg tid for 14 days	10 volunteers	Decreased imatinib $AUC_{0-\infty}$, C_{max}, and $t_{1/2}$	Induction of CYP3A4 and or P-glycoprotein	
Indinavir (85)	SJW (extract standardized to 0.3% hypericin) 300 mg tid for 16 days	6 males 2 females	Decreased indinavir AUC (57%)	Induction of CYP3A4	Low plasma concentrations of protease inhibitors are a cause of antiretroviral resistance and treatment failure
Irinotecan (90)	SJW (Bio Nutrition Health Products, The Netherlands) 300 mg tid for 18 days	2 males 3 females All cancer patients	Decrease (42%) plasma levels of SN-38 (the active metabolite of irinotecan)	Induction of CYP3A4	The decreased plasma levels of SN-38 may have a deleterious impact on treatment outcome
Ivabradine (83)	Jarsin®, 300 mg tid for 14 days	6 males 6 females	Decreased ivabradine AUC and C_{max}	Induction of CYP3A4	No pharmacodynamic effect was observed
Mephenytoin (23)	SJW (extract standardized to 0.3% hypericin and 4% hyperforin) 300 mg tid for 14 days	12 males	Increased urinary excretion of mephenytoin metabolites	Induction of CYP2C19	SJW affects the pharmacokinetics of other CYP2C19 substrates such as omeprazole and voriconazole
Methadone (109)	Jarsin®, 900 mg/daily for 31 days	2 males 2 females All addict patients	Decreased methadone plasma concentration	Induction of CYP3A4 and/or P-glycoprotein	Possibility of a withdrawal syndrome
Mycophenolic acid (64)	Jarsin®, 300 mg bid for 14 days	6 males 4 females All transplant patients	No changes in mycophenolic acid pharmacokinetics	None	Mycophenolic acid is not a CYP or P-glycoprotein substrate
Midazolam (22)	Extract standardized to 0.3% hypericin, 900 mg single dose or 300 mg tid for 14 days	8 males 5 females	Decreased oral midazolam AUC after long term (14 days) but not short term (1 day) SJW administration	Selective induction of intestinal CYP3A	The therapeutic manifestation of such interaction was not determined

Table III. (continued)

Prescribed drug (reference)	SJW extract, dosage/duration	Sample size	Clinical result of interaction	Possible mechanism	Comments
Midazolam (18)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	6 males 6 females	Increased (98%) hydroxymidazolam/ midazolam serum ratios	Strong induction of CYP3A4 (sexual dimorphysm greater increase in female than in males)	
Midazolam (25)	LI160, 300 mg tid for 12 days	10 males 10 females	Increased midazolam clearance (more evident after oral administration)	Induction of intestinal and hepatic CYP3A4	
Midazolam (28)	Commercial extract (Rexall-Sundown Pharmaceutical, Boca Raton), 300 mg tid for 21 consecutive days during the second menstrual cycle and for 21 consecutive days during the third menstrual cycle	12 females	Increased oral (but not systemic) clearance of midazolam	Selective induction of intestinal CYP3A4	
Midazolam (27)	Unspecified extract, 300 mg tid for 10 days	20 males 8 females	Decreased plasma concentration of midazolam	Induction of intestinal and hepatic CYP3A4	
Midazolam (17)	Extract standardized to hypericin 0.3%, 300 mg tid for 28 days	6 males 6 females	Increased hydroxymidazolam/ midazolam serum ratios	Induction of CYP3A4	
Midazolam (42)	Six preparation containing different amounts of hyperforin, 2.68–41.25 mg hyperforin/daily for 14 days	42 males	Decreased midazolam AUC (maximal effect for extracts with high hyperforin content)	Induction of CYP3A4	
Midazolam (43)	Extract containing low hyperforin content (0.06 mg/capsule mg) 1 capsule (500 mg) bid for 14 days	20 males	Slight decreased midazolam AUC_{0-8}. No change in midazolam C_{max}, $t_{1/2}$, and T_{max}	Weak or no effect with SJW extracts containing low amounts of hyperforin	
Midazolam (29)	TruNature®, 300 mg tid for 14 days	12 healthy volunteers	Increased apparent oral clearance of midazolam	Induction of CYP3A4	
Nevirapine (44)	SJW (2 g infusion bid for 14 days, low amount of hyperforin)	36 females	No effect on nevirapine half-life	No enzymatic induction (CYP3A4 and CYP2B6) with SJW tea containing low amounts of hyperforin	SJW may render ineffective nevirapine if used at therapeutic dosage
Nifedipine (80)	Extract standardized to 0.3% hypericin and 5% hyperforin, 300 mg tid for 14 days	5 males 5 females	Decreased nifedipine $AUC_{0-\infty}$	Induction of CYP3A4	The therapeutic manifestation of such interaction has been not determined
Omeprazole (30)	Extract standardized to hypericin 0.3%, 300 mg tid for 14 days	12 males	Decreased omeprazole $AUC_{0-\infty}$ and C_{max}	Induction of CYP2C19	SJW affects the pharmacokinetics of other CYP2C19 substrates such as mephenytoin and voriconazole
Oral contraceptive (ethinylestradiol, norethindrone) (28)	Commercial extract (Rexall-Sundown Pharmaceutical, Boca Raton), 300 mg tid for 21 consecutive days during the	12 females	Increased clearance of norethindrone and reduction in the half-life of ethinylestradiol;	Induction of CYP3A4	Changes in the pharmacokinetic of oral pill can result in reduced efficacy and Increased breakthrough bleeding. No

	second menstrual cycle and for 21 consecutive days during the third menstrual cycle		increased breakthrough bleeding		effect was observed in a trial in which a SJW extract with low hyperforin was used (45)
Oral contraceptive (ethinylestradiol, desogestrel) (68)	Ze 117, Jarsin®, 300 mg tid for 21 consecutive days during the second menstrual cycle and for 21 consecutive days during the third menstrual cycle	18 females	Decreased AUC_{0-24} and C_{max} of 3-ketodesogestrel, but not of ethinylestradiol; increased intracyclic bleeding	Induction of CYP3A4	
Oral contraceptive (ethinylestradiol, norethindrone) (69)	Extract standardized to 0.3% hypericin and 3.7% hyperforin, 300 mg tid for eight weeks (during cycles 3 and 4)	16 females	Increased metabolism of norethindrone and ethinylestradiol Increased breakthrough bleeding	Induction of CYP3A4	
Oral contraceptive (ethinylestradiol, desogestrel) (45)	Ze 117, 250 mg bid for 14 days	26 females	No changes in oral contraceptive pharmacokinetics	No enzymatic induction with an extract with low hyperforin content	
Phenprocoumon (77)	LI160, 300 mg/daily for 11 days	10 males	Decreased phenprocoumon AUC (17.4%)	CYP induction	The decreased plasma levels of phenprocoumon could be clinically relevant
Pravastatin (78)	TruNature®, 300 mg tid for 14 days	8 males	No significant effect on plasma pravastatin levels	None	Pravastatin is not a CYP or P-glycoprotein substrate
Prednisone (66)	Extract standardized to 0.3% hypericin, 300 mg tid for 28 days	8 males	No changes in prednisone pharmacokinetics	None	One case of maniac episode has been reported (65)
Quazepam (94)	TruNature®, 300 mg tid for 14 days	13 males	Decreased C_{max} and AUC_{0-48}	Induction of CYP3A4	Physicians should be aware of this interaction when treating patients with quazepam
Simvastatin (78)	TruNature®, 300 mg tid for 14 days	8 males	Decreased plasma levels of simvastatin	Induction of CYP3A4 and/or P-glycoprotein	The therapeutic manifestation of such interaction was not determined
Tacrolimus (64)	Jarsin®, 300 mg bid for 14 days	6 males 4 females	Decreased AUC_{0-12} of tacrolimus, but not of mycophenolic acid	Induction of CYP3A4 and/or P-glycoprotein	Physicians should be aware of this interaction because of risk of rejection episodes
Tacrolimus (63)	Extract containing 440 μg hypericin/300 mg extract, 300 mg tid for 18 days	8 males 2 females	Decreased tacrolimus AUC	Induction of CYP3A4 and/or P-glycoprotein	
Talinolol (38)	Jarsin®, 300 mg tid for 12 days	9 males	Reduction of talinolol AUC after oral administration	Induction of intestinal P-glycoprotein	SJW is known to affect the pharmacokinetic of P-glycoprotein probes
Theophylline (115)	TruNature®, 300 mg tid for 15 days	12 males	No significant changes in theophylline pharmacokinetics	None	Although this study reported negative results, a case of decreased theophylline levels in a patient taking SJW has been reported (114)
Tolbutamide (22)	Extract standardized to 0.3% hypericin, 900 mg single dose or 300 mg tid for 14 days	8 males 5 females	No effect on tolbutamide pharmacokinetics	No effect on CYP2C9	SJW does not modify the pharmacokinetics of CYP2C9 probe drugs

Table III. (continued)

Prescribed drug (reference)	SJW extract, dosage/duration	Sample size	Clinical result of interaction	Possible mechanism	Comments
Tolbutamide (21)	Esbericum®, 1 capsule (60 mg extract) bid for 10 days	15 males 13 females	Marginal influence on tolbutamide pharmacokinetics	Weak or no effect on CYP2C9. However, an extract with low hyperforin content has been used	
Verapamil (81)	Movina®, 300 mg tid for 14 days	8 males	Decreased AUC (78–80%) of R- and S-verapamil	Induction of intestinal CYP3A4	Physicians should be aware of this interaction
Voriconazole (40)	LI160, 300 mg tid for 14 days	16 males	Increased AUC (22%) after 10 h, decreased AUC (59%) after 14 days SJW	CYP2C19 modulation	SJW affects the pharmacokinetics of other CYP2C19 substrates such as omeprazole and mephenytoin
Warfarin (76)	SJW, a tablet tid for 2 weeks (each tablet contained standardized dry extract equivalent to 1 g *H. perforatum* flowering herb top, 0.825 mg hypericin, and 12.5 mg hyperforin)	12 males	Increased warfarin clearance and decreased INR	Induction of CYP3A4 and possibly other CYP isoforms	The decreased plasma levels of warfarin could be clinically relevant

AUC area under the plasma concentration/time curve, *bid* twice daily, *tid* three times daily, *quid* four times, *CYP* cytochrome, C_{max} maximum plasma concentration times daily, T_{max} time to maximum plasma concentration, *SJW* St John's wort, *INR* international normalized ratio, *CYP* cytochrome P450

Antihyperlipidemic Drugs

The statins simvastatin and atorvastatin are metabolized by CYP34 and are also substrates for P-glycoprotein. Thus, there are clear possibilities for drug interaction with SJW. Accordingly, clinical studies have shown that SJW decreased plasma levels of simvastatin (but not pravastatin, which is not a substrate for CYP3A4 or P-glycoprotein) in healthy volunteers (78) and reduced the efficacy of atorvastatin in hypercholesterolemic patients (79). Specifically, SJW significantly increased the serum level of LDL cholesterol compared with control and increased the total cholesterol level (79). Physicians and patients should be aware of these interactions, and if treatment with SJW is considered necessary, then there may be a need for increasing the dose of statins.

Calcium Blockers

Nifedipine and verapamil, well-known calcium channel blockers used in the treatment of hypertension, are both metabolized by CYP3A. Clinical studies have shown that SJW decreased the AUC of both nifedipine (80) and verapamil (81) in healthy volunteers. The effect of SJW on verapamil bioavailability is caused by induction of first-pass CYP3A4 metabolism, most likely in the gut (81).

Beta Adrenergic Blockers

Talinolol is a beta1-adrenergic blocker used in essential hypertension and as an antiarrhythmic drug. Experimentally, talinolol is mostly used as a nonmetabolized *in vivo* probe for P-glycoprotein. In a controlled, randomized study (n=9), a 12-day SJW treatment resulted in a 93% increase in oral clearance and a 31% reduction in AUC. Renal and nonrenal clearance (CLNR), elimination half-life ($t_{1/2}$), peak serum drug concentration ($C_{\max}$), and time to reach $C_{\max}$ ($T_{\max}$) were not significantly modified (38). SJW affected only CLNR of i.v. talinolol. The effects of SJW on oral talinolol pharmacokinetics were associated with increased MDR1 messenger ribonucleic acid (mRNA) as well as P-glycoprotein levels in the duodenal mucosa (38). It was concluded that SJW has a major inductive effect on intestinal P-glycoprotein (38).

Antianginal Drugs

Ivabradine belongs to a new class of antianginal drugs, which have recently become available: the selective and specific I(f) inhibitors. The mode of action of this novel class involves selective and specific inhibition of the major pacemaker current in the sinoatrial node, the mixed sodium/potassium current (I(f)), which results in pure heart rate reduction (82). Ivabradine is extensively metabolized by intestinal and hepatic CYP3A4. A clinical study performed in healthy volunteers showed that administration of SJW significantly decreased ivabradine maximal plasma concentration (33 *vs* 15 ng/mL) and AUC (144 *vs* 44 ng h/mL) (83).

Cardiac Inotropic Drugs

Digoxin, a cardiac glycoside which originates from the *Digitalis* (foxglove) plant, is used in the treatment of heart failure. Drug interaction studies with digoxin are important because of its narrow therapeutic index. Digoxin is a substrate of P-glycoprotein. Two trials have shown a decreased in plasma concentration of digoxin following SJW administration (35,36). The effect occurred after at least 10-day coadministration (35), although the possibility that such interaction occurs after a treatment of less than 10 days cannot be ruled out (no time course of the digoxin plasma concentration was provided in the original papers). In accordance with an intestinal induction of P-glycoprotein, interaction was characterized by a reduction in AUC_{0-24} and C_{max}, which lead to a reduction in C_{trough} (36). Although the decreased of digoxin levels is believed to be clinically relevant, no therapeutic interactions between St John's wort and digoxin have been reported to date.

Anti-HIV Drugs

Antiretroviral drugs, widely used to treat HIV infections, include protease inhibitors such as indinavir and nonnucleoside reverse transcriptase such as nevirapine. Clinical trials have shown that SJW may interact with antiretroviral drugs leading to drug failure (84). An open-label study showed a large (AUC_{0-8} decreased by 57%) reduction in the plasma concentration of indinavir (CYP3A4 and P-glycoprotein substrate) in six healthy volunteers taking SJW (85). One spontaneous case has been reported in the UK, in which the patient experienced an increase in HIV RNA viral load following the concomitant use of SJW and indinavir or lamivudine (86). Finally, de Maat and colleagues reported increased oral clearance of nevirapine (nonnucleoside reverse transcriptase inhibitor) following SJW wort coadministration in five HIV patients (87). Nevirapine metabolism is catalyzed by CYP3A4 and CYP2B6 (88).

Anticancer Drugs

In recent years, the use of herbal products in cancer patients has increased significantly, even concomitantly to conventional chemotherapeutic treatment (89). Considering the narrow therapeutic window of anticancer drugs, this use increases the risk of clinically relevant herb–anticancer drug interactions (89).

In an unblinded, randomized crossover study, five cancer patients were treated with irinotecan (a known substrate for CYP3A4 employed in the treatment of colorectal cancer) in the presence and absence of SJW (90). It was found that the plasma levels of the active metabolite SN-38 decreased by 42% following SJW cotreatment. Consequently, the degree of myelosuppression was substantially worse in the presence of SJW.

Two trials investigated the effect of SJW on the pharmacokinetics of imatinib—a potent inhibitor of the Bcr-Abl and c-kit tyrosine kinases that promote tumor cell proliferation. Imatinib is metabolized mainly by CYP3A4 and transported by P-glycoprotein, both induced by SJW. Both studies found increased imatinib clearance following SJW administration (91,92), suggesting that the herb may compromise the efficacy of the anticancer agent.

Benzodiazepines

The benzodiazepines alprazolam and midazolam are used experimentally as probe for CYP3A4 activity because they are entirely metabolized by intestinal and hepatic CYP3A4. Consistently, a number of clinical trials have shown that SJW decreased plasma levels of alprazolam (20) and midazolam (17,18,22,25,28,29,42) in healthy volunteers. Such effect is not observed with low hyperforin-containing extracts (21) or after a short (i.e., 3 days) period (19) of treatment. Quazepam is a short-acting benzodiazepine with significant effect on the induction and maintenance of sleep without major effect on sleep architecture (93). It is metabolized by both CYP3A4 and CYP2C19, which are both induced SJW. Accordingly, SJW, compared to placebo, decreased quazepam C_{max} and $AUC_{(0-48)}$ in 13 healthy subjects (94).

Another anxiolytic drug which may interact with SJW is buspirone. Theoretically, the concomitant use of buspirone (5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptor agonist) and SJW (inhibitor of 5-HT reuptake) may lead to an additive/synergistic effect on 5-HT signaling. A possible serotonin syndrome after combination of buspirone and SJW has been reported in a 27-year-old female with symptoms of generalized anxiety disorder (95). Moreover, a 42-year-old female patient with a history of mild traumatic brain injury and resulting depression experienced hypomania after adding SJW and ginkgo to her regimen of buspirone and fluoxetine (a 5-HT reuptake inhibitor) (96). Remission was observed after discontinuation of the herbal medicines.

Antidepressant Drugs

Selective serotonin reuptake inhibitors (SSRI) are a class of antidepressant used in the treatment of depression, anxiety, and personality disorders. They inhibit selectively the neuronal reuptake of 5-HT, leading to increased levels of the neurotransmitter available to bind the postsynaptic 5-HT receptor(s). Case series and case reports have shown that SJW interacts with 5-HT reuptake inhibitors such as paroxetine, sertraline, venlafaxine, and nefazodone resulting in symptoms of a central serotonin syndrome (97–99). Characteristic symptoms observed include mental status changes, tremor, autonomic instability, gastrointestinal upset, headache, myalgias, and motor restlessness. SSRI do not appear to be metabolized by CYP enzymes or P-glycoprotein. In these cases, a pharmacodynamic mechanism is postulated to be involved since both SJW and SSRI inhibit 5-HT reuptake.

A case of manic episode in a 28-year-old man taking both SJW and sertraline has been reported (100). According to the report reliability scale for drug interaction, the case was classified as possible (101), although it was complicated by concomitant testosterone replacement therapy following bilateral orchidectomy. It is unlikely that testosterone replacement itself could have contributed directly to the maniac episode, since plasma testosterone level was below the normal physiological range, despite replacement therapy (100).

The possible interaction between amitriptyline—a tricyclic antidepressant which may be used in depressive illness of psychotic or endogenous nature and in selected patients with neurotic depression—and SJW has been evaluated in an open-label trial (n=12 depressed patients). SJW significantly decreased the amitriptyline and nortriptyline AUC by 22% and 41%, respectively. Cumulative urinary amounts of amitriptyline and metabolites decreased to the same extent as plasma concentrations upon SJW comedication (102). Amitriptyline clearance is primarily dependent on metabolism by a variety of CYP enzymes. Demethylation to nortriptyline proceeds with CYP2C19 and CYP3A; additionally, amitriptyline is a P-glycoprotein substrate.

Antiepileptic Drugs

The antiepileptic agent mephenytoin is primarily metabolized by CYP2C19. An open-label, placebo-controlled, crossover trial found that SJW increased the urinary 4′-hydroxymephenytoin excretion in CYP2C19 wild-genotype subjects, whereas no significant alteration was observed for CYP2C19 poor metabolizers (23). Another antiepileptic drug which has been evaluated for possible pharmacokinetic interaction with SJW is carbamazepine. Perhaps surprisingly, Burstein and colleagues found no significant differences before or after the administration of SJW in carbamazepine, a CYP3A4 substrate, and carbamazepine-10,11-epoxide peak concentration, trough concentration, AUC, or oral clearance (103). It should be noted, however, that carbamazepine is also metabolized by other CYP isoforms, such as CYP2C8 (104). On the other hand, treatment of carbamazepine for 7 days resulted in a significant decrease of plasma concentration of pseudohypericin (105), one of the active ingredients of SJW (12,13). Although the effect was considered marginal, this trial reports an unusual case of interaction in which a synthetic drug affects the pharmacokinetics of an herbal extract active ingredient.

Anesthetic Drugs

Widespread use of herbal medications among the presurgical population may have a negative impact on perioperative patient care. Consequently, patients are asked to discontinue herbal product before surgery (106). A case of delayed emergence has been reported in a 21-year-old woman (107). Anesthesia was induced by fentanyl and propofol and maintained with sevoflurane in oxygen and nitrous oxide. Using this treatment, total anesthesia time usually persists for approximately 10 min. Thirty minutes later, the patient was not roused, even when she was subjected to painful stimulation. At 90 min postanesthesia, the patient was easily rousable, with spontaneous eye opening. On the recovery, she denied taking any benzodiazepine, barbiturate, narcotic, or cannabinoid preoperatively, but she stated to have taken SJW for the preceding 3 months for depression on the advice of a herbalist. She had also increased the recommended dose after several weeks because of perceived lack of antidepressant effect. The mechanism of such interaction is presently unknown.

A possible cause of cardiovascular collapse during anesthesia has been reported in a 23-year-old woman (108). General anesthesia was induced with fentanyl and propofol; *d*-tubocurarine and succinylcholine were used as muscle relaxants. Shortly after anesthesia induction, the patient became hypotensive, and subsequently, the patient was found to be weakly responsive to adrenergic vasopressors such as ephedrine and phenylephrine. In the recovery room, after the patient had fully emerged from anesthesia, she stated to have taken SJW for depression on a daily basis for the past 6 months. Before her previous surgery, she had not been taking SJW. Causality and mechanism of such interaction are unknown, although the authors speculated that SJW might theoretically reduce the expression of adrenergic receptors (108).

Drugs Used in Addicted Patients

Methadone is used in the controlled withdrawal of addicts from heroin. Methadone is mainly metabolized by CYP3A4, which is induced by St John's wort. SJW reduced methadone concentration-to-dose ratios in four addict patients (109). Two patients reported symptoms that suggested a withdrawal syndrome. Bupropion is the first nonnicotine-based drug for smoking cessation (110). It exerts its effect primarily through the inhibition of dopamine reuptake into neuronal synaptic vesicles. A prolonged orofacial dystonia in a 58-year-old female following therapy with bupropion and SJW has been reported (111). The patient presented dystonic movements affecting the right side of her face, neck, and right arm. Her only other medications were SJW, which she had been taking for several years, and hormone replacement therapy. SJW inhibits the reuptake of a number of neurotransmitters, including dopamine. Thus, an additive effect on dopamine reuptake inhibition, making dopaminergic side effects, such as dystonia, is believed likely to occur in this case.

A case of serotonin syndrome resulting from coadministration of SJW and tryptophan, which a 19-year-old man used to "detox" himself from ecstasy, has been reported. Although it is unclear when he discontinued using ecstasy, his clinical presentation was temporally consistent with serotonin syndrome shortly after initiating self-directed therapy with tryptophan and SJW (112). Tryptophan is the precursor of 5-HT and hence might increase its brain levels.

Central Muscle Relaxant Agents

Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasms and the resulting pain or discomfort. Two clinical trials, by the same authors, found an increase in hydroxychlorzoxazone/chlorzoxazone serum ratios, which is suggestive of CYP2E1 induction. The effect was found to be more pronounced in young rather than in elderly subjects (17,18).

Drugs Acting on the Respiratory System

Despite having been recognized for a long time as a cheap and effective therapy for the treatment of asthma and chronic obstructive pulmonary disease, theophylline is relegated to third-line therapy in the treatment of airway diseases due to the drug's frequent side effects and relatively low

efficacy (113). Theophylline is mainly metabolized by CYP1A2, CYP2E1, and CYP3A4. A case of decreased plasma levels of theophylline after taking SJW has been reported (114). This resulted in an increased dosage of theophylline to achieve therapeutic concentration. However, such possibility of interaction has been not confirmed by a clinical trial, in which it was shown that a 15-day administration of SJW did not affect the plasma and urine level of theophylline (115).

Fexofenadine is a nonsedating H1-receptor—selective, long-acting antihistaminic drug. Experimentally, fexofenadine is used as probe substrate for P-glycoprotein. Two clinical trials showed that SJW affected the pharmacokinetics of fexofenadine (25,27). Dresser and colleagues found that 12 days' treatment with SJW increased the oral clearance of fexofenadine in 21 young healthy subjects (25). In a different study, Wang and colleagues reported that a single dose of SJW significantly increased the maximum plasma concentration of fexofenadine by 45% and significantly decreased the oral clearance by 20%, with no change in half-life or renal clearance. Long-term administration of SJW did not cause a significant change in fexofenadine disposition relative to the untreated phase. Compared with the single-dose treatment phase, long-term SJW wort caused a significant 35% decrease in maximum plasma concentration and a significant 47% increase in fexofenadine oral clearance (27).

Finally, multiple clinical trials (19,20,22,24,26) have shown that SJW did not affect the pharmacokinetics of dextromethorphan, a highly effective and widely used nonopioid antitussive drug.

Hypoglycemic Drugs

Tolbutamide is a CYP29 substrate which is therapeutically used in the management of type II diabetes. Two clinical trial showed that 10- or 14-day treatment with SJW did not alter tolbutamide AUC, C_{max}, and T_{max} (21,22). CYP2C9 is also the major contributor to the hypoglycemic drug gliclazide metabolism. A crossover controlled study was conducted in 21 healthy subjects, who received gliclazide either alone or during 15 days treatment with SJW. The study found that SJW significantly altered gliclazide pharmacokinetics—revealed by a decreased gliclazide AUC, $t_{1/2}$, and apparent oral clearance—in all except for four healthy subjects (116). There were no significant changes in glucose or insulin $AUC_{(0-4)}$ after SJW treatment and no significant differences according to CYP2C9 genotype. Thus, treatment with SJW significantly increases the apparent clearance of gliclazide which is independent of CYP2C9 genotype. People with diabetes receiving this combination should be closely monitored to evaluate possible signs of reduced efficacy. The different effects of SJW on pharmacokinetics of oral tolbutamide and gliclazide could be due the potential contribution of CYP2C19 allelic variants.

Antimicrobics

Voriconazole is a triazole antifungal developed for the treatment of life-threatening fungal infections in immunocompromised patients. Voriconazole has a nonlinear pharmacokinetic profile with a wide inter- and intraindividual variety (117). The extensive metabolism of voriconazole is primarily mediated by CYP2C19 and CYP3A as well as by CYP2C9 to a lesser extent. In a controlled, open-label study, SJW slightly increased (after 10-h SJW intake) and strongly reduced (after 15-day SJW intake) voriconazole AUC (40).

The antibiotic drug erythromycin is a commonly used CYP3A4 probe for *in vivo* phenotypic enzyme activity evaluation using ^{14}C erythromycin breath test. The test is performed by administering a trace amount of ^{14}C-labeled erythromycin and thereafter evaluating the amount of exhaled $^{14}CO_2$. Consistent with the ability of St John's wort to induce CYP3A4, Dürr and colleagues found a 40% increase in the activity of hepatic CYP3A4 (37).

Antimigraine Drugs

Eletriptan is a second-generation 5-$HT_{1B/1D}$ receptor agonist indicated for the acute treatment of migraine (118). A case of serotonin syndrome and rhabdomyolysis induced by concomitant use of eletriptan, fluoxetine, and SJW has been reported in a 28-year-old woman (119). The patient was admitted to hospital for sudden head deviation with loss of consciousness. On admission, she had been taking fluoxetine for 1 year and self-prescribed SJW pills for 1 month. In the previous 3 days before admission to hospital, she had taken eletriptan to treat recurrent migraine. The authors believe that SJW and fluoxetine predisposed the patient to develop serotonin syndrome precipitated by subsequent use of eletriptan.

Drugs Acting on the Gastrointestinal Tract

Omeprazole is a well-known proton pump inhibitor widely used for the treatment of various acid-related gastric disorders. *In vivo*, omeprazole is metabolized mainly by CYP3A4 and CYP2C19 to two major metabolites, 5-hydroxyomeprazole and omeprazole sulfate. CYP2C19 is the predominant enzyme involved in the 5-hydroxylation reaction, whereas CYP3A4 is the major enzyme-mediating sulfoxidation of omeprazole (120). After a 14-day treatment with SJW, substantial decreases in plasma concentrations of omeprazole were observed in a randomized crossover study (n=12 healthy volunteers). SJW increased omeprazole sulfone and 5-hydroxyomeprazole C_{max} and $AUC_{0-\infty}$. Thus, SJW induced both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole (30).

Loperamide is an antidiarrheal medication approved for the control of diarrhea symptoms and is available without a prescription. It is a phenylpiperidine derivative with a chemical structure similar to opiate receptor agonists that does not cross the blood–brain barrier (121). A brief episode of acute delirium, possibly induced by exposure to SJW, valerian, and loperamide has been reported (122). The mechanism of this interaction is presently unknown.

CONCLUSIONS

As far as we today know, St John's wort represents the herbal product which is most involved in herb–drug interactions (8). Clinical evidence suggests that SJW may cause both pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions arise when SJW is combined

with drugs which are CYP (3A4, 2E1, 2C19) and/or P-glycoprotein substrates. Among these, interactions between SJW and cyclosporine or anti-HIV drugs may have serious clinical consequences. Hyperforin is the chemical ingredient of SJW responsible for P-glycoprotein and cytochrome induction (21,46). Pharmacodynamic interactions may occur when SJW is combined with drugs which enhance 5-HT signaling in the brain. For example, SJW has been shown to cause serotonin syndrome when combined with serotonin reuptake inhibitors or with 5-HT receptor agonists. Healthcare professionals need to be aware of potential interactions between SJW and prescribed medicines.

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