REVIEW ARTICLE

Drug Safety 2004; 27 (11): 773-797
0114-5916/04/0011-0773/$31.00/0

Drug Interactions with St John's Wort
Mechanisms and Clinical Implications

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Contents

Abstract

The purpose of this paper is to review preclinical and clinical evidence relating to drug interactions with preparations of the medicinal herb St John's wort (*Hypericum perforatum*). A systematic literature search was carried out in three electronic databases up to June 2004. Information about case reports classified as St John's wort drug interactions was retrieved from the WHO Collaborating Centre for International Drug Monitoring and from the UK Medicines and Healthcare products Regulatory Agency in June 2003.

Against the background of proven efficacy in mild to moderate depressive disorders and an excellent tolerability profile in monotherapy, there is sufficient evidence from interaction studies and case reports to suggest that St John's wort may induce the cytochrome P450 (CYP) 3A4 enzyme system and the P-glycoprotein drug transporter in a clinically relevant manner, thereby reducing efficacy of co-medications. Drugs most prominently affected and contraindicated for concomitant use with St John's wort are metabolised via both CYP3A4 and P-glycoprotein pathways, including HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors (only CYP3A4), the immunosuppressants ciclosporin and tacrolimus, and the antineoplastic agents irinotecan and imatinib mesylate. Efficacy of hormonal contraceptives may be impaired as reflected by case reports of irregular bleedings and unwanted pregnancies. Drugs with a narrow therapeutic index should be monitored more closely when St John's wort is added, discontinued or the dosage is changed. The St John's wort constituent hyperforin is probably responsible for CYP3A4 induction via activation of a nuclear steroid/pregnane and xenobiotic receptor (SXR/PXR) and hypericin may be assumed to be the P-glycoprotein inducing compound, although the available evidence is less convincing.

Combinations of St John's wort with serotonergic agents and other antidepressants should be restricted to prescription-only, by experienced clinicians, due to potential central pharmacodynamic interactions.

In conclusion, providing certain precautions and contraindications are followed, and adequate information is given to healthcare professionals and patients, the safe and effective use of quality-tested St John's wort products can be ensured.

Preparations of St John's wort (*Hypericum perforatum*) have been used for centuries in traditional medicine to treat depressive and anxious states, nervousness, restlessness, sleep disorders and other illnesses.[1] During the last 2 decades, clinical efficacy of hydroalcoholic St John's wort extracts at a daily dose of 500–1800mg has reliably been shown in mild to moderate depressive disorders, as reflected by a series of current systematic reviews and meta-analyses.[2-7] In 1997, the Drug Commission of the German Medical Association included St John's wort preparations matching certain quality standards in their recommendations for the treatment of depression.[8] Furthermore, the American College of Physicians – American Society of Internal Medicine recommended St John's wort for the treatment of acute mild depression in their guidelines published in 2000.[7] Other data from clinical trials and re-analyses of depression studies suggest that St John's wort may be helpful in treating somatoform disorders,[9,10] premenstrual syndrome,[11] obsessive-compulsive disorder,[12] anxiety disorders,[13-15] alcohol withdrawal,[16] and depressive and hyperactive children and adolescents.[17] The total plant extract is still valid as the active substance and potent CNS effects have been demonstrated mainly for constituents belonging to the groups of naphthodianthrones (i.e. hypericins), phloroglucinols (i.e. hyperforins) and flavonol glycosides, with hyperforin playing an important role.[18,19]

St John's wort preparations are characterised by a favourable safety profile, lacking cardiac adverse

effects[20] and sedating properties,[21] and having no negative impact on cognition, car driving and other complex tasks.[22] Rare adverse drug reactions (ADRs) include mild gastrointestinal irritability, insomnia, dizziness and skin reactions related to UV light exposure in sensitive individuals (photosensitivity; caused by hypericin).[23] Reviews of St John's wort clinical trial data reveal substantially lower figures for ADR frequencies and withdrawals due to ADRs when compared with other antidepressants,[24] and long-term treatment seems not to be detrimental to the safety profile.[25] Furthermore, figures from spontaneous reporting schemes are very low, even when taking considerable under-reporting into account which may be more common with St John's wort preparations than for synthetic antidepressants due to the prescription-free availability of St John's wort products.[26]

In 1997, Kerb et al. published the first human data of an increased urinary 6-β-hydroxy-hydrocortisone/hydrocortisone ratio after 14 days intake of St John's wort, suggesting an induction effect of St John's wort on cytochrome P450 (CYP)3A4.[27] In the years 1999 and 2000, case reports of pharmacokinetic drug interactions with St John's wort, i.e. those resulting in significant decreases in blood concentrations of ciclosporin and consecutive transplant rejection, were published and created great interest.[28,29] Drug regulatory authorities issued warnings to medical professionals and consumers/patients, initiated pharmacovigilance procedures, demanded adjustments of product information and in some cases decreed changes in the registrational status of St John's wort products.[30-36]

During the last few years, a large number of studies have been initiated to investigate potential interactions of St John's wort with the absorption, metabolism and elimination of other drugs. Likewise, growing information has accumulated from published case reports and spontaneous reporting schemes.

The objectives of this paper are to review St John's wort drug interactions, their potential mechanisms and clinical relevance, and to suggest recommendations on the clinical use of St John's wort preparations.

1. Materials and Methods

A systematic literature search without language restrictions was carried out in the databases Medline, Embase and Ingenta up to June 2004, applying the following search terms: 'St John's wort', 'hypericum', 'hyperforin', 'hypericin', 'flavonoids', 'cytochrome', 'P450', 'MDR-1', 'p-glycoprotein', 'metabolism', 'interaction', 'induction' and 'inhibition'. Further relevant publications were identified by searching personal files, contacting colleagues engaged in the fields of herbal medicine and clinical pharmacology and by checking the reference lists of papers.

Data from the ADR database of the WHO Collaborating Centre for International Drug Monitoring, administered by the Uppsala Monitoring Centre were requested in June 2003. The national drug authority of the UK, the Medicines and Healthcare products Regulatory Agency (MHRA), was contacted individually, since a considerable number of spontaneous case reports were published by this authority and the MHRA does not allow the WHO Collaborating Centre for International Drug Monitoring to release the full case reports from the UK.

Data were analysed and classified as case reports from pharmacovigilance, case reports from the literature, human pharmacokinetic studies with comedications or with model substrates of metabolic and elimination pathways, and mechanistic studies (preclinical, animal and human), and summarised comprehensively in tables.

To avoid duplicates and artefacts of too high case numbers, published case reports that could be identified as being derived from the reporting schemes of drug regulatory authorities that report to the WHO Collaborating Centre for International Drug Monitoring were excluded from the listing and from the evaluation of 'case reports from literature'.[2,37-40]

Publications of St John's wort phase II-IV trials did not report any adverse reactions recognised as drug interactions.

2. Results

2.1 Case Reports from Pharmacovigilance

The listing received from the ADR database of the WHO Collaborating Centre for International

Table I. Records from the adverse drug reaction database of the WHO Collaborating Centre for International Drug Monitoring, classified as St John's wort drug interactions (date of retrieval, 16 June 2003)[a]

Drug category	Co-medication (n)	Adverse reaction (n)
Pharmacodynamic interactions (n = 16)		
Antidepressants	Paroxetine (4)	Serotonin syndrome (2); cardiac death (1); other (1)
	Fluoxetine (1)	Hypertension (1)
	Citalopram (1)	Transient collapse (1)
	Clomipramine (1)	Serotonin syndrome (1)
	Nefazodone (1)	Hypertonia, abnormal thinking, chest pain (1)
	Venlafaxine (1)	Oculogyric crisis, dizziness, confusion, asthenia, fever (1)
	Moclobemide (1)	Hallucinations (1)
Analgesics	Tramadol (2)	Serotonin syndrome (2)
Migraine therapeutics	Sumatriptan (1), zolmitriptan (1)	Myocardial infarction (2)
Anaesthetics	Fentanyl + propofol + sevoflurane (1)	Excessive sedation (1)
CNS stimulants	Methylphenidate (1)	Depression, aggression, agitation, concentration ↓ (1)
Pharmacokinetic interactions (n = 86)		
Hormonal contraceptives	EE/levonorgestrel (11)	Irregular bleeding (7); unwanted pregnancy (4)
	EE/desogestrel (10)	Irregular bleeding (7); unwanted pregnancy (3)
	EE/gestodene (3)	Irregular bleeding (2); unwanted pregnancy (1)
	EE/norgestimate (3)	Irregular bleeding (2); unwanted pregnancy (1)
	EE/norethisterone (2)	Irregular bleeding (1); unwanted pregnancy (1)
	Levonorgestrel (4)	Unwanted pregnancy (4)
	Norethisterone (1)	Unwanted pregnancy (1)
	Etonogestrel, subcutaneous (1)	Unwanted pregnancy (1)
	Not further specified (2)	Irregular bleeding (1); unwanted pregnancy (1)
Anticoagulants	Phenprocoumon (11)	Drug effect ↓ (9); drug effect ↑ (2)
	Warfarin (14)	Drug effect ↓ (9); drug effect ↑ (5)
Immunosuppressants	Ciclosporin (6)	Drug level/effect ↓ (6); transplant rejection (1)
	Tacrolimus (1)	Drug level/effect ↓ (1)
Thyroid hormones	Thyroxine (4)	Drug effect ↓ (3); drug level ↓ (1)
Hormonal replacement therapy	Not further specified (2)	Fatigue (1); vaginal haemorrhage (1)
HMG-CoA reductase inhibitors	Atorvastatin (2)	Drug effect ↓ (2)
Various	Citalopram (1)	Drug level ↑ (1)
	Lithium salt (1)	Drug level ↓ (1)
	Theophylline (1)	Drug level ↓ (1)
	Amoxicillin (1)	Drug effect ↓ (1)
	Indinavir + lamivudine + stavudine (1)	Drug effect ↓ [HIV viral load ↑] (1)
	Zuclopenthixol (1)	Drug effect ↓ [schizophrenia aggravated] (1)
	Verapamil (1)	Drug effect ↓ [SV tachycardia aggravated] (1)
	Methotrexate (1)	Drug effect ↓ [psoriasis aggravated] (1)
	Dipyridamole (1)	Drug effect ↓ [transient ischaemic attack] (1)
Interactions not classified (n = 6)		
Various	Enalapril (1)	Insomnia, tachycardia (1)
	Cod liver oil (1)	Burning sensation (1)
	Hypericum extract (1)	Eye burns (1)
	Potassium iodide (1)	Hypaesthesia, taste loss (1)
	Omeprazole (1)	Chronic indigestion (1)

Continued next page

Table I. Contd

Drug category	Co-medication (n)	Adverse reaction (n)
	Ciprofloxacin + dihydrocodeine/ paracetamol (acetaminophen) + prednisolone + furosemide + omeprazole + indometacin (1)	Agitation, depressed level of consciousness, dizziness, extrasystoles, palpitations, tachycardia (1)

a Spain, Austria, Belgium, and the UK do not allow WHO to release full case reports to the public. Case reports from the UK were received directly from the Medicines and Health Products Regulatory Agency. Considerable overlap with cases in table II must be assumed.

EE = ethinylestradiol; **SV** = supraventricular; ↓ = decrease; ↑ = increase.

Drug Monitoring comprised a total of 67 case reports from eight countries (Australia, n = 6; Canada, n = 3; Germany, n = 14; Ireland, n = 2; New Zealand, n = 5; Sweden, n = 13; Switzerland, n = 23; South Africa, n = 1) classified as drug interactions with St John's wort mono-preparations, as of 16 June 2003 (table I). Reports pertaining to fixed combinations of St John's wort with other herbs (n = 3) were not taken into account. Records from Austria, Belgium, Spain and the UK were not part of the WHO listing, since the drug safety bodies of these countries do not allow WHO to release case reports. Therefore, reports from the UK (n = 41) were directly received from the MHRA 'Yellow Card' scheme as of 2 June 2003.

The WHO emphasises that the information is not homogenous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and that the information does not represent the opinion of the WHO. Sources, as well as the proportions of reports, vary greatly over time and from country to country and may be influenced by the extent of use of St John's wort products, publicity, nature of the reactions and other factors. Moreover, no information is provided on the number of patients exposed to St John's wort products. In the vast majority of cases, sufficient information to reliably estimate interaction likelihood is lacking (e.g. in only three cases outcome of dechallenge and rechallenge are reported), and most cases would have to be classified as 'unevaluable' according to a 10-point scoring system recently suggested by Fugh-Berman and Ernst.[41]

Thus, information from these reports must be assessed cautiously and should be seen as a trigger for further research activities, rather than as a standalone source of decision making.

Sorting reports by 'date of onset of ADR', a time course paralleling the publicity of the topic, is as follows: 1997, n = 1; 1998, n = 7; 1999, n = 23; 2000, n = 15; 2001, n = 7; 2002, n = 7. In the UK listings, date of onset and date of report of cases are not given. However, Barnes et al. stated in their recent St John's wort review that the MHRA had received 35 reports of suspected St John's wort drug interactions until September 2000,[2] and the 'Yellow Card' scheme listed only six more cases as of June 2003.

Pharmacodynamic interactions with antidepressants (mainly resulting in serotonin syndrome or hypertension) and pharmacokinetic interactions with hormonal contraceptives, anticoagulants and immunosuppressants, account for 79% of the reports listed in table I.

Except for one record of phototoxicity after co-administration of St John's wort and delta-aminolaevulinic acid for photodiagnosis,[42] reports of pharmacodynamic interactions all pertain to centrally acting agents, with serotonin syndrome-like symptoms being the most prominent adverse reactions, when St John's wort and other serotonergic agents like selective serotonin reuptake inhibitors (SSRIs) or tramadol were combined.

Nearly all pharmacokinetic interactions reported resulted in reduced blood concentration or reduced therapeutic response of co-medications. Solely for anticoagulants, in 7 of 25 reports, an increase in drug effect was observed.

2.2 Case Reports from Literature

For the most part, scientific publications of St John's wort drug interactions reasonably resemble the figures from pharmacovigilance. A total of 92 cases, led by interactions with antidepressants and immunosuppressants, which account for 77% of re-

Table II. Case reports of St John's wort drug interactions from literature, except cases reported and published from pharmacovigilance systems[a]

Co-medication	Adverse reaction	Subjects (n)	References
Pharmacodynamic interactions (n = 15)			
Sertraline, paroxetine, nefazodone, venlafaxine, fenfluramine, buspirone	Symptoms of serotonin excess (serotonin syndrome)	9	46-49
Paroxetine	Sedation, weakness, drowsiness	1	50
Sertraline, testosterone	Mania	1	51
Loperamide, valerian	Delirium	1	52
Fentanyl + propofol + D-tubocurarine + suxamethonium chloride (succinylcholine) + isoflurane	Hypotension under general anaesthesia	1	53
Fentanyl + propofol + sevoflurane	Delayed emergence after general anaesthesia	1	54
Delta-amino-laevulinic acid	Phototoxicity (skin reactions)	1	42
Pharmacokinetic interactions (n = 86)			
Ciclosporin	↓ Ciclosporin plasma concentration; need for exceptionally high ciclosporin dosage; organ rejection (n = 6)	62	29,43-45,55-62
Nevirapine	Mean increase of nevirapine oral clearance by 35%	5	63
Hormonal contraceptives	Irregular bleeding (n = 1); unwanted pregnancy (n = 3)	4	64-67
Methadone	↓ Methadone trough concentrations by 47% (n = 2); symptoms of methadone withdrawal (n = 2)	4	68
Tacrolimus	↓ Tacrolimus plasma concentrations	1	69
Theophylline	Theophylline plasma concentration more than doubled after discontinuation of St John's wort	1	70

a Considerable overlap with cases in table I must be assumed.

↓ = decrease.

ports, are listed in table II. Interestingly, no cases of suspected interactions with anticoagulants could be retrieved from the literature. Moreover, significantly fewer interactions with hormonal contraceptives were published in scientific journals when compared with pharmacovigilance reporting figures. This observation may be explained by the fact that women affected by irregular bleeding or unwanted pregnancy rarely seek help at academic centres. On the other hand, 45 cases of the more serious interaction with the immunosuppressant ciclosporin were observed in one clinic alone, which were obviously not reported to the appropriate drug regulatory authority in equivalent numbers.[43] Rejection of the transplanted organ was reported in 6 of the 62 reports of decreased ciclosporin blood concentrations due to St John's wort co-administration.[29,43-45]

Two well documented small case studies of reduced blood levels of the HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (n = 5)[63] and of methadone (n = 4)[68] add valuable information not emerging from pharmacovigilance.

2.3 Human Pharmacokinetic Studies with Co-Medications

Since the first observations made by Kerb et al. in 1997,[27] a series of phase I studies investigating the effect of St John's wort administration on the pharmacokinetics of co-medicated drugs have been carried out.

Summarising, area under the concentration time curve (AUC) of co-medications that are mainly metabolised via the CYP3A4 pathway (e.g. simvastatin[71]) and of those additionally eliminated via the drug transporter P-glycoprotein (e.g. ciclosporin,[72] tacrolimus,[73] irinotecan,[74] imatinib,[75] verapamil[76] or the HIV-protease inhibitor indinavir[77]) were decreased 30–80% by co-administration of St John's wort. Less distinct decreases in blood concentrations were observed for drugs

predominantly eliminated via other CYP enzymes (e.g. amitriptyline,[78] warfarin[79] or phenprocoumon[80]) or via P-glycoprotein alone (e.g. digoxin[81-88]) with the exception of omeprazole, the AUC of which was decreased by 38% and 44% in CYP2C19 mutant and wild genotypes, respectively.[89] The AUC of the partial CYP3A4 substrate quazepam was decreased significantly by 25% after 14 days of St John's wort 900 mg/day, but pharmacodynamic assessments were not influenced by St John's wort in this study.[81]

Interestingly, St John's wort co-medication over 14 days did not alter carbamazepine pharmacokinetics. Carbamazepine is predominantly inactivated via CYP3A4 oxidation, but is also a potent inducer of CYP3A4 itself. Since carbamazepine trough concentrations remained stable on days 19, 20, 21 and 22 of administration (prior to addition of St John's wort), the authors concluded that St John's wort was not able to further induce CYP3A4 activity after auto-induction by carbamazepine was complete.[90]

Pharmacokinetic parameters of mycophenolic acid and of pravastatin, neither of which are metabolised via CYP and P-glycoprotein, were not changed by co-administration with St John's wort.[71,73]

More difficult to interpret are the results from three interaction studies with oral contraceptives. In one study, St John's wort 900mg daily was added for two menstrual cycles to an ethinylestradiol/norethisterone (norethindrone) combination pill. Follicle stimulating hormone (FSH), luteinising hormone (LH) and progesterone concentrations on days 11–16 of the menstrual cycle were not altered by St John's wort administration, thereby indicating a lack of ovulation. However, oral clearances of norethisterone and of midazolam (CYP3A4 model substrate) increased significantly by 16% and 53%, respectively, and accordingly, 7 of 12 volunteers experienced break-through bleeding during month 3, compared with 2 of 12 subjects in month 1.[82] In two other studies, ethinylestradiol/desogestrel combination pills were investigated.[83,84] Eighteen women who exhibited ovulation in a pre-study cycle received 600mg and 900mg St John's wort extract LI-160 daily in two consecutive cycles, after a baseline cycle without co-medication. Serum estradiol, progesterone and ethinylestradiol were not significantly altered, whereas AUC of 3-keto-etonogestrel was reduced by 44%. Thirteen and 15 women experienced breakthrough bleeding under the two St John's wort dosages compared with six women without co-medication, but vaginal endosonography revealed no changes in follicle maturation.[83] Sixteen women who were stable for at least 3 months on the pill, received a 14-day treatment with St John's wort 500mg daily in the other study. Ethinylestradiol and 3-keto-etonogestrel pharmacokinetics remained unaltered and no bleeding irregularities were observed. Further, activities of CYP2D6, CYP2C19 and CYP3A4 did not differ between days 7 and 21.[84]

Digoxin, although also a model substrate of P-glycoprotein mediated drug transport, is reported in this section since this drug is frequently prescribed. In four of the five digoxin studies, 10–14 days' treatment with 900mg daily of the St John's wort extract LI-160 reliably resulted in a moderate decrease of digoxin AUC by 18–27%.[84-86,88] Lower doses of St John's wort of 500mg (ZE-117) and 320mg (esbericum) daily for 10 and 14 days, respectively, did not alter the pharmacokinetic profile of digoxin.[84,87] In another study, 14 days' treatment with 900mg St John's wort extract LI-160 was compared with 500–4000mg St John's wort crude drug powder, 1200mg St John's wort oil and 1600mg St John's wort tea. Drug powder dosed to 4000mg (roughly comparable to 900mg St John's wort LI-160, based on a mean drug/extract ratio of 4.5 : 1) and 2000mg resulted in significant decreases of digoxin AUC by 27% and 18%, whereas St John's wort LI-160 caused a 25% decrease. All other preparations and doses left digoxin AUC unchanged.[88]

2.4 Human Pharmacokinetic Studies with Model Substrates

The majority of drugs and other xenobiotics, such as food constituents, exhibit lipophilic characteristics to promote passage through biological membranes and subsequently gain access to their site of action. Transformation into more hydrophilic metabolites is therefore essential for their elimination from the body and termination of their biological activity. Phase I biotransformation reactions introduce or expose enzymatically a functional group on the parent compound, which generally results in

pharmacological inactivation. Phase II enzymatic reactions form highly polar conjugates with endogenously derived glucuronic acid, sulphate, glutathione, amino acids or acetate, that can be rapidly excreted in the urine and faeces.[91]

The CYP mono-oxygenase system is the most important phase I metabolising enzyme system, responsible for the inactivation of a wide range of exogenous and endogenous (e.g. corticosteroids) compounds. It is mainly located in the liver, in enterocytes and the kidney, and isoforms CYP3A, CYP2D and CYP2C account for the metabolism of 50, 25 and 20%, respectively, of the currently known drugs.[92] Other enzymes, like esterases and hydrolases, play a minor role in phase I metabolism.[91]

More recently, transporter proteins located in cell membranes have gained interest in relation to drug distribution and elimination. An important representative from this group seems to be the efflux transporter P-glycoprotein, which is encoded by the multidrug resistance-1 (*MDR-1*) gene. P-glycoprotein is present in the liver, kidney, at the blood-brain barrier and at several other sites, and constitutes, along with intestinal CYP metabolism, an important part of the biochemical barrier function of the intestinal mucosa.[93]

A considerable number of human studies have assessed the impact of St John's wort treatment on the pharmacokinetics of various model substrates of drug metabolism and elimination.

2.4.1 Cytochrome P450 (CYP) 3A4

The metabolism of the endogenous CYP3A4 substrate hydrocortisone has been found to be significantly induced after 14 days' treatment with daily doses of St John's wort 900mg in four studies[27,81,94,95] and with St John's wort 1800mg in another study.[96] Further evidence for significant induction of CYP3A4 by St John's wort derives from studies applying midazolam as a model substrate. While a single dose of St John's wort did not alter midazolam pharmacokinetics,[97] repeated administration of St John's wort 900 mg/day for 10–60 days consistently resulted in changes of pharmacokinetic parameters representing relevant CYP3A4 induction.[82,97-100] Furthermore, increased midazolam metabolism by St John's wort co-administration was found to be more significant in females compared with males in a small sample,[100] but did not differ across six ethnic subgroups of volunteers (White, Black, Hispanic, Chinese, Indian and Malay).[99] Except in one study,[82] metabolism of midazolam was also significantly increased after intravenous administration, although to a lesser extent than after oral administration. The authors concluded that St John's wort mediated induction of CYP3A4 in the intestine is of at least the same importance as induction in the liver.[97-99] Two other studies further corroborated observations of CYP3A4 induction by St John's wort, using nifedipine[101] and the ^{14}C-erythromycin breath test[86] as specific substrate and probe, respectively. In three studies, no significant effect of St John's wort treatment on the pharmacokinetics of CYP3A4 substrates dextromethorphan[102] (partial substrate only; mainly metabolised via CYP2D6) and alprazolam[87,103] were seen. In two of these studies, St John's wort 900 mg/day was applied for only 3–4 days[103] and for 8 days.[102] In the third study, St John's wort was administered for 10 days, however, at the relatively low daily dose of 320mg.[87] However, in one study utilising alprazolam, significant 2-fold reductions of AUC and oral clearance were seen after 14 days' administration of 900mg LI 160 daily, with no apparent differences between the sexes.[104]

2.4.2 CYP2D6

Dextromethorphan is mainly metabolised via CYP2D6 to dextrorphan and was used in five studies to investigate the impact of St John's wort on CYP2D6 activity.[95,97,102-105] In all of the dextromethorphan studies, St John's wort was given at 900mg daily and no significant changes in the urinary dextromethorphan/dextrorphan ratio was observed.

Debrisoquine is hydroxylated via CYP2D6 to 4-hydroxy-debrisoquine, but is also a P-glycoprotein substrate, and was assessed in one study with a St John's wort co-medication of 900 mg/day for 28 days. A moderate increase in the urinary 4-hydroxy-debrisoquine/debrisoquine ratio by 23% was reported.[100]

2.4.3 CYP1A2

Serum ratios of caffeine and its metabolite paraxanthine were investigated in five studies to evaluate the impact of St John's wort on CYP1A2 metabolism.[87,95,97,100,106] Low dose St John's wort (320 mg/day) over 10 days[87] and a single dose of 900mg St John's wort, [97] as well as repeated dosing for 8 days[106] and for 14 days,[97] left serum ratios of caffeine/paraxanthine, and AUC caffeine and paraxanthine, unchanged. Only in one study was a moderate but significant increase of paraxanthine/caffeine ratio by 26% reported, after 28 days of St John's wort treatment at 900 mg/day.[100] In another caffeine study, CYP1A2 activity seemed to be slightly increased only in females.[95]

2.4.4 CYP2C9

Two studies using tolbutamide as a model substrate for CYP2C9 activity did not reveal significant changes by St John's wort co-treatment.[87,97]

2.4.5 CYP2C19

Beside sulfoxidation via CYP3A4, omeprazole is 5-hydroxylated predominantly by CYP2C19; as a result, omeprazole was suggested to be utilised as a specific CYP2C19 probe.[107] In a human volunteer study applying St John's wort 900 mg/day for 14 days, AUC of omeprazole decreased by approximately 40%. 5-Hydroxy-omeprazole was significantly increased by 37% in CYP2C19 wild, but not in mutant genotypes.[89]. Both warfarin and amitriptyline are metabolised to a significant extent via CYP2C19[108,109] and slight but significant decreases of plasma concentrations of these drugs were shown in studies with St John's wort co-medication.[78,79,107-109]

2.4.6 CYP2E1 and N-Acetyltransferase

Of the other phase I biotransformation enzymes CYP2E1 was significantly induced, as reflected by an increase of 110% in the 6-hydroxy-chlorzoxazone/chlorzoxazone ratio after 28 days' treatment with St John's wort 900mg daily,[100] and N-acetyltransferase activity was not affected by 8 days and 14 days of St John's wort co-medication at 900 mg/day.[95,106]

2.4.7 UDP-Glucuronosyltransferase

UDP-glucuronosyltransferase is the only phase II biotransformation enzyme investigated and its activity seems not to be affected by St John's wort treatment. In one study, the proportion of the glucuronidated active irinotecan metabolite SN-38 and unconjugated SN-38, was not changed by 18 days treatment with 900mg St John's wort per day.[74] In two other studies, a 14-day treatment with 900mg and 1800mg St John's wort LI 160 daily did not alter the daily urinary excretion of D-glucaric acid in 50 and 48 volunteers, respectively.[27,96]

2.4.8 P-Glycoprotein

Besides the interaction studies with the P-glycoprotein substrate digoxin reported in the preceding section, another four studies have been published which investigated the impact of St John's wort treatment on the pharmacokinetics of the P-glycoprotein substrates fexofenadine,[98,99,110,111] and talinolol.[112] In two studies, fexofenadine oral clearance and fexofenadine AUC were substantially increased and reduced, respectively,[98,99] as was the talinolol AUC reduced in another study,[112] each after 10[99] and 12 days[98,112] of treatment with St John's wort 900 mg/day. Interestingly, in another study, although fexofenadine maximum plasma drug concentration (C_{max}) was significantly increased and fexofenadine oral clearance significantly decreased after a single dose of 900mg St John's wort, no changes regarding these parameters were seen after a 14-day treatment with 900mg St John's wort when compared with the baseline situation.[110,111] As with CYP3A4 induction, increased fexofenadine elimination via P-glycoprotein did not differ across six ethnic subgroups of volunteers (White, Black, Hispanic, Chinese, Indian and Malay).[99]

2.5 Mechanistic Studies

A large variety of studies investigated genetic expression, protein content or activity of CYP enzymes and P-glycoprotein in humans, rodents and cell cultures.

2.5.1 Human studies

Two rather small human studies both found P-glycoprotein (1.4- and 1.6-fold) and CYP3A4 expression (1.5- and 2.4-fold) to be increased in duodenal biopsies of volunteers.[86,113] However, no changes of P-glycoprotein expression in peripheral blood lymphocytes was demonstrated in the one

study,[113] while P-glycoprotein expression showed a distinct 4.2-fold increase and P-glycoprotein mediated rhodamine-123 efflux was doubled in human lymphocytes after 1800mg St John's wort daily for 16 days in another study.[114]

Utilising the ^{13}C-lactose ureid breath test, orocoecal transit time remained unchanged after a 13-day treatment with 900mg St John's wort LI 160 daily in ten volunteers, thereby ruling out considerable decreases of absorption due to shortened intestinal transit.[115]

2.5.2 Animal Studies

Three rodent studies found hepatic CYP3A activity and/or protein content significantly increased to comparable extents (2- to 6-fold) after oral treatment with St John's wort extracts from 140 mg/kg up to 1000 mg/kg.[86,116,117] Doses of 140 mg/kg and 240 mg/kg revealed this effect after a 3-week treatment, but not after one and two weeks in Swiss Webster mice,[116] while 600 mg/kg effected significant hepatic CYP3A induction after a 4-day treatment in male CD1 mice.[117] The St John's wort constituent hyperforin, dosed equivalent to a content of 3% and 6% in the total extract, dose-dependently induced hepatic CYP3A activity to an extent comparable to St John's wort total extract after 4 days of oral treatment.[117] However, intestinal CYP3A2 expression was found to be unchanged after administration of 1000mg St John's wort LI 160 for 14 days in male Sprague-Dawley rats.[86]

Similar to the effects on CYP3A, hepatic CYP2E1 activity and expression was increased 2- to 2.5-fold after 3 weeks, but not after 1–2 weeks, of treatment with St John's wort extract 120–240 mg/kg in Swiss Webster mice.[116]

In the same species, intraperitoneal application of St John's wort extract 280 mg/kg, hyperforin 10 mg/kg and hypericin 1 mg/kg for 4 days left total hepatic CYP450 content, and activities and protein levels of CYP1A2, CYP2E1 and CYP3A, unaltered.[118] Route of administration, differences between rodent species and short duration of treatment may give an explanation for the negative results.

No significant changes in any activity or microsomal protein content of various hepatic enzymes were found after a 10-day oral treatment of Sprague-Dawley rats, neither by two hydroalcoholic St John's wort extracts (300 mg/kg), nor by the St John's wort constituents hyperforin, hypericin, biapigenin or hyperin.[119]

One study found intestinal P-glycoprotein expression to be substantially increased 3.8-fold (1000 mg/kg St John's wort LI 160, 14 days) and hepatic P-glycoprotein expression unchanged in male Sprague-Dawley rats,[86] another could not demonstrate a significant impact of a 7-day treatment with St John's wort extract 300 mg/kg on intestinal P-glycoprotein expression in the same species.[120]

A drug transporter protein family, which is also involved in the elimination of P-glycoprotein substrates like digoxin and fexofenadine, the organic anion transporting polypeptides (Oatp), were investigated regarding their inducibility by St John's wort treatment in male Sprague-Dawley rats. Hepatic Oatp2 expression was increased 4-fold after treatment with St John's wort extract 1000mg and 5.8-fold after dexamethasone 40 mg/kg for 14 days each, while hepatic Oatp1 and Oatp4 as well as intestinal Oatp3 expression remained unaffected.[121]

2.5.3 Cell Culture Studies

In contrast to observations from case reports and from clinical studies, a series of *in vitro* studies revealed potent inhibition of activities of various CYP enzymes by both St John's wort extracts and a variety of St John's wort constituents, which will not be discussed here.[122-128] In most cases, the inhibition is of a competitive nature suggesting that the St John's wort constituents may serve as CYP substrates and that *in vivo* they may also have the potential to induce CYP expression, provided that the required intracellular concentrations can be attained.[129]

In fact, significant induction of CYP3A4 expression by five different St John's wort extracts and by 1 μmol/L hyperforin[130,131] and of CYP1A2 by two different St John's wort extracts[132,133] were demonstrated in cell cultures of human hepatocytes,[131,133] human hepatocellular carcinoma (HepG2) cells,[130] and in human colon cancer (LS180) cells.[132] Beside significant induction of CYP3A4 and CYP1A2, another study also showed at least 3-fold increases in the activity of CYP1A1, CYP2B6, epoxide hydrolase, and glutathione S transferase by 0.6 μmol/L

hyperforin in human hepatocytes.[134] One study applying St John's wort extract ZE 117 found no changes of CYP3A4 expression in human colorectal cancer (Caco-2) cells.[113]

Concentration-dependant induction of P-glycoprotein expression by two different St John's wort extracts and by hypericin was reported from experiments in Caco-2 cells[113] and in LS180 cells.[126,135] Another St John's wort extract (not further specified) activated the P-glycoprotein mediated efflux of digoxin across Madine-Darby Canine Kidney cells in a concentration-dependant manner, but inhibited digoxin efflux at high St John's wort concentrations.[136]

2.5.4 Receptor Mechanisms

To elucidate the mechanisms underlying induction of CYP enzymes, five studies investigated the influence of St John's wort and St John's wort constituents on the function of members of a nuclear receptor family of ligand-activated transcription factors that are thought to regulate CYP gene expression via binding to response elements in CYP gene promoters.[137]

One study found a 1.8- to 5.2-fold increase of xenobiotic response element (XRE)-mediated chloramphenicol acetyltransferase (CAT) activity, pointing to induction of CYP1A2 via this mechanism.[70] Another study revealed closely similar results.[133] However, hypericin concentrations required to achieve this effect ranged from 10–125 μmol/L, which is at least 100-fold above the maximum plasma hypericin concentrations observed in volunteers who were treated with 1800mg of St John's wort extract LI 160, containing 0.3% hypericin.[138]

Three different St John's wort extracts and hyperforin, but not 11 other St John's wort constituents, significantly activated pregnane X receptor (PXR) and related enzyme function in a concentration-dependant manner. The concentration of hyperforin required to produce 50% of the maximum drug effect (EC_{50}) was 23 nmol/L and hyperforin competitively bound with high affinity to PXR (concentration required to produce 50% inhibition [IC_{50}] was 27 nmol/L).[131] Since hyperforin plasma levels may peak to approximately 1 μmol/L after administration of 1200mg of a St John's wort extract containing 5% hyperforin in humans,[139] these findings may translate into changes of enzyme activities of clinical relevance.

Another group corroborated these results by observing a similar concentration-dependant activation of steroid X receptor (SXR) by crude St John's wort extract and hyperforin, but not by hypericin.[140] PXR-mediated induction of CYP2C9 by hyperforin at a concentration as low as 0.2 nmol/L has also been reported recently for the first time.[141]

3. Summary and Discussion

3.1 Pharmacodynamic Drug Interactions

Combinations of two or more drugs with similar or overlapping pharmacodynamic properties may result in an excess of the pertaining pharmacodynamic effects. Resulting adverse reactions have been reported for combinations of St John's wort with antidepressants, other centrally acting drugs and the photosensitiser delta-amino-laevulinic acid (table I and table II). St John's wort is thought to exert its antidepressant activity partly via significant central re-uptake inhibition of serotonin and modulation of central serotonin receptor density and function.[18,19] Serotonin syndrome has been reported in sensitive patients with St John's wort monotherapy[142] and, as expected, in combination with other serotonergic agents like antidepressants or tramadol.

Whether two cases of myocardial infarction after a St John's wort combination therapy with a triptan can be attributed to the addition of St John's wort is questionable. Triptans act as agonists at serotonin $5\text{-}HT_{1B/D}$ autoreceptors which results in functional 5-HT antagonism and potent vasoconstriction. They are contraindicated in patients with a history of ischaemic or vasospastic coronary artery disease or uncontrolled hypertension, but no precautions are normally recommended to be followed regarding combinations with serotonergic agents.[143]

Combinations of centrally acting agents always imply the risk of unforeseeable reactions. This may be true for co-treatments of St John's wort with antidepressants, anaesthetics and methylphenidate (table I and table II) as well as with other psychoactive drugs. Quality and frequency of regarding reports do not pose specific risks for St John's wort co-medication.

Hypericin, a photosensitising constituent in St John's wort, may rarely cause phototoxic skin reactions in sensitive individuals.[18] Therefore, an increased risk for such reactions must be considered when St John's wort is combined with other photosensitising agents (table II).

3.2 Pharmacokinetic Drug Interactions

Numerous clinical observations of decreased blood concentrations or therapeutic responses of drugs co-administered with St John's wort, point to induction of metabolism and/or elimination mechanisms by the herb.

The results from some *in vitro* studies showing mostly competitive inhibition of various CYP enzymes by St John's wort extracts and constituents, tend to contradict this. However, such *in vitro* observations cannot be extrapolated confidently to the *in vivo* situation, since inhibition may reflect nothing more than competitive inhibition by constituents present in the extract. Constituents *in vivo* may also have the potential to induce CYP expression, provided that the required intracellular concentrations can be attained. Little is known about the human bioavailability and metabolism of St John's wort constituents. Metabolites and constituents not considered important to date may contribute to pharmacological effects by agonistic, antagonistic or synergistic mechanisms. Therefore, translations of *in vitro* findings to the clinical situation must be evaluated critically.

3.2.1 CYP3A4 and P-Glycoprotein

Summarising the results of St John's wort interaction studies, there is sufficient evidence that St John's wort may induce hepatic and intestinal CYP3A4 and intestinal P-glycoprotein. In particular, drugs that are metabolised and eliminated by both CYP3A4 and P-glycoprotein, like ciclosporin, tacrolimus, irinotecan, imatinib, verapamil and indinavir, seem to be significantly affected. Although CYP3A4 and P-glycoprotein display a considerable overlap in substrate specificities,[144] the bioavailability of compounds metabolised via CYP3A4 but not eliminated via P-glycoprotein, like midazolam and nifedipine,[144] may also be significantly reduced by St John's wort co-administration. It seems to be rather unlikely that St John's wort treatment will result in interactions of clinical relevance with drugs predominantly eliminated via P-glycoprotein (e.g. digoxin, talinolol, fexofenadine). Decreases of plasma AUC in studies were rather small and no corresponding clinical observations have been reported from literature or pharmacovigilance reports. This may not be surprising when considering talinolol and fexofenadine, but is of particular importance with digoxin, since this drug is frequently prescribed and blood concentrations are regularly monitored.

3.2.2 Other CYPs and Metabolising Enzymes

There is some evidence from one human and one animal study that CYP2E1 may be substantially induced by St John's wort.[100,116] However, CYP2E1 plays only a minor role in drug metabolism and only inhalative anaesthetics are primarily metabolised via CYP2E1.[145,146] However, the two cases relating to a drug interaction of St John's wort, with among others sevoflurane, reported excessive sedation and delayed emergence, indicating rather a pharmacodynamic interaction. Theophylline is also, to some extent, metabolised via CYP2E1,[147] which may partially explain the observation of doubled theophylline plasma levels after withdrawal of St John's wort in one case.[70] However, the patient was administered 11 additional medications, some of them known to interact with theophylline, and only one further case of decreased plasma levels under St John's wort co-treatment is reported from pharmacovigilance, although theophylline is frequently prescribed and blood concentrations are monitored regularly.

More striking, theophylline pharmacokinetics remained unchanged after 14 days' treatment with St John's wort 900mg in a randomised clinical interaction study.[148] Oxidative theophylline inactivation is mainly mediated by CYP1A2[149] and the impact of St John's wort on this CYP enzyme remains unclear. Induction of CYP1A2 expression by St John's wort extract and hyperforin was demonstrated in experiments utilising human cell cultures.[132-134] However, two human studies applying St John's wort at a dose of 900mg daily for a sufficient duration of 14 and 28 days revealed divergent results. One study reported a moderate but significant increase of caffeine/paraxanthine ratio by 26%,[100] the other found

caffeine AUC and metabolic ratio unchanged.[97] In another human study, CYP1A2 appeared to be induced only in females.[95] Two other volunteer studies revealed no changes, one with the low St John's wort dose of 320mg daily,[87] the other after 8 days of treatment with 900mg daily.[106] Concentration-dependant increase of CYP1A2 activity, mediated via a XRE – a transcriptional enhancer sequence present in the gene promoters of CYP1A2 – by hypericin in two *in vitro* studies are doubtful, since hypericin concentrations required were at least 100-fold above levels achieved in humans when treated with typical doses of St John's wort extract.[70,133]

There is good evidence from a total of five human studies that CYP2D6 is not relevantly affected by St John's wort treatment.[97,100,102-105] The only pertinent finding, a moderately increased metabolic ratio of debrisoquine may be explained by the fact that debrisoquine is also eliminated via P-glycoprotein.[100] Studies investigating CYP2C9 *in vitro* produced contradictory results.[134,141] Two human CYP2C9 interaction studies revealed no impact of St John's wort treatment.[87,97] On the other hand, several cases of reduced efficacy of oral anticoagulants (table I) and a clinical study with warfarin[79] suggest that CYP2C9 and also CYP2C19 may be affected. Moreover, significantly decreased plasma concentrations of amitriptyline and omeprazole,[78,89] which both are considerably metabolised via CYP2C19,[107,109] imply that St John's wort treatment may relevantly induce this enzyme.

Hepatic conjugation with glucuronic acid remained unchanged in three human studies.[27,74,96]

3.2.3 Mechanisms of Interactions and Contribution of Single St John's Wort Constituents

A common mechanism for the effects of St John's wort on CYP enzymes and drug transporters may be the activation of the orphan nuclear receptor SXR/PXR by hyperforin.[131,140,141] This receptor is an important component of the body's adaptive defence mechanisms against endogenous and exogenous potentially toxic substances. It does not only regulate expression of CYP3A4 and CYP2C9, but also of a variety of other CYP and phase I and phase II biotransformation enzymes and drug transporters.[150,151] However, the extent to which enzymes and drug transporters were induced by St John's wort extracts and hyperforin varied substantially, with CYP3A4 being by far the enzyme most significantly affected.[134] Hypericin and other St John's wort constituents did not activate SXR/PXR.[131,140] Hypericin increased XRE mediated CYP1A2 activity, however, this was at doses probably too high to achieve clinical relevance.[70,133] More striking are the results from a study showing 3- to 7-fold induction of P-glycoprotein expression in LS180 cells by hypericin doses of 0.03–3 μmol/L which are to be expected in the human gut after typical St John's wort administration.[135] In contrast, hyperforin did not reveal significant induction of P-glycoprotein expression in human hepatocytes[134] and one may postulate different mechanisms for the two St John's wort constituents regarding CYP3A4 and P-glycoprotein induction. This assumption may be substantiated by the observation that St John's wort ZE 117, which is practically devoid of hyperforin,[152] significantly induced P-glycoprotein expression and reduced ciclosporin uptake in Caco-2 cells,[113] but needs confirmation by further *in vivo* studies involving hypericin and hypericin-free St John's wort extracts.

The role of other constituents in this context is largely unclear. Several St John's wort flavonoids inhibited CYP enzymes *in vitro*,[122,124,125,128] pointing to their role as pertaining substrates. On the other hand, various St John's wort flavonoids did not activate PXR,[131] and studies on enzyme expression are lacking. Flavonoids are ubiquitous in the plant kingdom and are known to interact with P-glycoprotein[153,154] and to modulate most CYPs, in particular CYP3A4.[155] Further *in vivo* studies are needed to elucidate the role of St John's wort flavonoids in St John's wort drug interactions.

The majority of high quality St John's wort products contain St John's wort extract manufactured by means of 80% methanol (methyl-alcohol) or 50–60% ethanol (alcohol) with a comparable profile of constituents in most cases.[156] The only well-known exception pertains to St John's wort extract ZE 117, which lacks significant amounts of hyperforin.[152] No interactions with digoxin and with a ethinylestradiol/desogestrel combination contraceptive are reported from two human studies with 500mg daily of this extract;[84] however, studies

involving more significant CYP3A4 substrates are lacking. In contrast, duodenal expression of CYP3A4 and P-glycoprotein was significantly induced in volunteers,[113] P-glycoprotein expression in Caco-2 cells was increased,[113] and three cases of pharmacokinetic interactions with other drugs were reported from Switzerland.

Unfortunately, the composition of many St John's wort products tested in interaction studies is not characterised sufficiently to perform neat comparisons with results from other trials with other St John's wort products. The provision of extraction solvent, drug/extract ratio and contents of hypericins, hyperforins and total flavonoids, as well as assessments of serum levels of at least hypericin and hyperforin, would allow for a more substantial discussion of the data and would help to explain disparate findings.

On the basis of the net effect of total St John's wort extracts on CYP and P-glycoprotein function, no particular product can currently be estimated to provide a more favourable interaction profile than one other.

Physicochemical factors affecting gastrointestinal absorption of drugs may be another source of drug interactions with St John's wort. Guinea-pig ileum motility was altered by St John's wort treatment in one study and the authors suggested an action of the St John's wort constituent hyperforin at gastrointestinal serotonin receptors.[157] However, oro-coecal transit time remained unchanged after a 13-day treatment with St John's wort 900 mg/day in volunteers, suggesting the absence of a relevant impact of St John's wort treatment on gastrointestinal motility in humans.[115]

A recent investigation found the formation of nano- and micro-particles and of precipitates in aqueous solutions of St John's wort extract with warfarin, resulting in a maximal reduction of 36.6% in the amount of free warfarin. The authors discuss that the interaction of St John's wort with oral anticoagulants may partly be caused by this mechanism.[158]

3.2.4 Dose-Response Relationships and Time Course

In particular, the discussion of dose-response relationships of St John's wort drug interactions is complicated by the variability of the composition of St John's wort products. Predictions appear to be impracticable for non-standardised products.

Looking at human studies involving CYP3A4 and P-glycoprotein substrates, where evidence of induction is most stable, it can be estimated that St John's wort treatment with doses from 900 mg/day of a typical hydroalcoholic extract for at least 10–14 days reliably results in significant induction. After 3–4 days of St John's wort 900 mg/day no effect on CYP3A4 was seen,[103] and after 8 days' treatment with St John's wort 900 mg/day only a trend for CYP3A4 induction was reported.[102] However, the reverse is not necessarily true. Duodenal P-glycoprotein and CYP3A4 expression was significantly increased after 7 days' treatment with St John's wort 750 mg/day in human volunteers[113] and ciclosporin dosage had to be raised in all 11 transplant patients from the third day of St John's wort co-administration at 600 mg/day according to the monitoring of ciclosporin blood concentrations.[72] Blood levels of nortriptyline, a CYP2C19/CYP3A4 metabolite of amitriptyline, were markedly decreased after only three days of St John's wort co-treatment.[78] From cell culture studies, as well as from clinical studies, a time course pattern of initially increased concentrations of co-medications after single-dose administration, followed by decreased drug concentrations after longer term St John's wort dosing can be noted. Different St John's wort constituents may be responsible for initial inhibition and later onset of induction of enzymes and drug transporters. Another explanation could be that primary inhibition of enzymes and transporters is consecutively overcome by high levels of protein.[159,160]

Clear reduction of tacrolimus blood concentrations was brought about by a daily dose of St John's wort 600mg.[73] It was found that 500mg daily of another St John's wort extract did not affect disposition of ethinylestradiol and digoxin.[84] Crude St John's wort powder dosed to 2000mg, which is approximately equivalent to 450mg of a typical hydroalcoholic St John's wort extract with a mean drug/extract ratio of 4.5 **:** 1, significantly decreased the AUC of the P-glycoprotein substrate digoxin, whereas 1000mg had no effect.[88] Finally, 10 days' treatment with 320 mg/day of a St John's wort extract beside others did not alter the

pharmacokinetics of the CYP3A4 substrate alprazolam.[87]

Thus, a lower dosage threshold for drug interactions cannot be clearly defined. For some clinical situations the threshold may be between approximately 300mg and 500mg St John's wort extract daily. The lower threshold of efficacy of St John's wort in depressive and somatoform disorders is likely to be 500–600mg daily.[2,5,9,18] Thus, reducing the dosage in order to substantially reduce interactions is likely to lead to a substantial loss of efficacy.

Drugs metabolised predominantly via CYP3A4 and P-glycoprotein at the same time, like ciclosporin, tacrolimus, irinotecan, imatinib, verapamil and indinavir, are probably affected at significantly lower St John's wort dosage, with an earlier onset. This assertion may further be explained by the well-documented report of decreased ciclosporin blood concentrations after the regular intake of a herbal tea mixture containing St John's wort.[56] St John's wort tea is known to be practically devoid of hyperforin and to contain only small amounts of hypericin; in fact, only flavonoids are recovered at >50%.[156]

3.2.5 Influence of Gender and Ethnicity

CYP3A4 and P-glycoprotein induction seems to be similar between various ethnic populations.[99] Whether gender is a factor influencing the extent of CYP3A4 induction, cannot be decided unequivocally to date. Gender-related analyses of results have been reported in four studies. Increases in urinary 6-hydroxy-hydrocortisone/hydrocortisone ratio were not different between male and female volunteers in two studies,[95,96] as well as altered alprazolam disposition in another study.[104] However, female subjects exhibited a 74% greater increase in 1-hydroxy-midazolam/midazolam ratios than male subjects in another study of small size (n = 6 per gender), and effects on other CYP enzymes were not different between sexes.[100] CYP1A2 activity appeared to be induced by St John's wort only in females (n = 8 per gender).[95]

3.2.6 Potency of St John's Wort in Comparison with Other Enzyme-Inducing Drugs

Although hyperforin activated SXR/PXR to a similar extent to rifampicin (rifampin),[131,140] CYP3A4 expression by hyperforin was about half of rifampicin in human hepatocytes.[134] In Swiss Webster mice, CYP3A4 and CYP2E1 induction was approximately doubled by the positive controls dexamethasone and acetone, respectively, when compared with St John's wort.[116] Hepatic CYP3A4 induction and decrease of oral digoxin AUC in volunteers were 1.4-fold and 18% by St John's wort compared with 3.5-fold and 37% by rifampicin.[86] While 6-β-hydroxy-hydrocortisone excretion is induced 5- to 10-fold by phenobarbital (phenobarbitone) and rifampicin,[161,162] St John's wort treatment resulted in a comparatively slight increase of about 50%.[96] Further, the enzyme inducing spectrum of St John's wort seems to be less broad than that of other CYP3A4 inducers. Whereas phenobarbital, phenytoin, carbamazepine or rifampicin treatment substantially increased urinary D-glucaric acid excretion,[163-165] St John's wort had no effect on this pathway.[96] After auto-induction was complete, carbamazepine metabolism could be further induced by phenobarbital and phenytoin,[166,167] but not by St John's wort.[90]

Thus, St John's wort may be a moderate CYP and P-glycoprotein inducer that has less pronounced effects on compounds not extensively metabolised pre-systemically and in cases where CYP enzymes are already induced.

3.2.7 CYP/P-Glycoprotein Induction as a Therapeutic Principle

According to more recent findings, mechanisms responsible for unwanted drug interactions also play an important role in the elimination of endogenous toxic substances and in the regulation of tissue formation. In that way, induction or inhibition of metabolising enzymes and drug transporters may serve as the pharmacological basis of new drug treatments.

For example, P-glycoprotein induction is believed to be part of the antidepressant action of St John's wort by eliminating increased hydrocortisone and corticosterone transport across the blood-brain barrier.[168]

Lately, β-amyloid, a polypeptide which is thought to contribute to the aetiology of Alzheimer's disease, was found to be eliminated from neurons by P-glycoprotein,[169] and deposition of Alzheimer's beta-amyloid was inversely correlated with P-glyco-

protein expression in the brains of elderly non-demented humans.[170]

Activation of SXR/PXR can protect the body against pathophysiological concentrations of toxic bile acids according to some investigations[171] and several lines of evidence suggest that these findings may have implications in the treatment of human cholestatic liver disease.[150]

Very recently, SXR/PXR has also been uncovered to play a key role in the regulation of bone homeostasis. Menatetrenone (vitamin K2) acts through SXR/PXR to favour the expression of osteoblastic markers and a subset of SXR/PXR activators may be effective in the treatment of osteoporosis.[172]

New or optimised treatments with St John's wort may emerge from these observations.

4. Clinical Implications

4.1 Pharmacodynamic Interactions

Although evidence is rather weak, the risk of developing serotonin syndrome and other central adverse reactions cannot be ruled out. Therefore, combinations of St John's wort with psychotropic medications, in particular with serotonergic drugs (e.g. SSRIs, tricyclic antidepressants, venlafaxine, tryptophan, tramadol, buspirone) and other antidepressants, should be used cautiously. Experienced therapists (e.g. psychiatrists) may apply such combinations, with greater attentiveness for typical symptoms.[173]

Three cases of interactions with St John's wort and drugs used in general anaesthesia (combinations of fentanyl, propofol, halogenated inhalative) indicate a possible risk of such combinations. The use of herbal medicines in the perioperative setting has been intensively discussed by anaesthesiologists.[174,175] There is general agreement that most patients using herbal remedies fail to report this use to their healthcare providers,[176] and therefore, anaesthesiologists should routinely obtain a history of herbal medicine use during the preoperative interview. Based on the elimination half-lives of hyperforin and hypericin, St John's wort preparations should be discontinued at the latest 5 days prior to elective surgery.[174]

Combinations of St John's wort with agents used for photodiagnostic procedures or for phototherapy are contraindicated due to the risk of severe phototoxicity. Doctors working in this field should regularly check whether their patients are using St John's wort preparations.

4.2 Pharmacokinetic Interactions

A characteristic of drug biotransformation is a large inter-individual variability that often results in marked differences in the extent of metabolism and elimination. A combination of genetic, environmental (exposure to exogenous compounds such as food ingredients) and disease-state factors account for this variability, and drug therapy of the future will be much more individualised, especially for drugs with a narrow therapeutic index.[91] Against this background, it is clear that drug interactions in most cases cannot be reliably predicted or excluded in the individual patient.

To evaluate the general clinical relevance of suspected St John's wort drug interactions it is crucial to assess each drug class and drug separately, since evidence from various parameters has to be considered: from case reports and interaction studies, the range of therapeutic index of the affected drug, clinical outcome and risks of reduced drug effect, availability and feasibility of drug level or drug effect monitoring, and costs of possible dose modifications.

4.2.1 Immunosuppressants

It has clearly been shown that bioavailability of the immunosuppressants ciclosporin and tacrolimus is decreased by St John's wort co-administration in a clinically relevant manner and that probably every patient is affected. Given the severe and even life-threatening risks that may arise from St John's wort interactions with these drugs, and that dosage adjustments would be very costly, the concomitant use of St John's wort should be contraindicated.

This is probably not true for the immunosuppressant mycophenolic acid, which was not affected in a clinical interaction study and is metabolised via pathways not suspected to interact with St John's wort.[73]

4.2.2 Anti-HIV Drugs

All HIV protease inhibitors share the same biotransformation pathways: breakdown by CYP3A4 and elimination via P-glycoprotein. HIV NNRTIs are all metabolised extensively via CYP3A4, but are probably not transported by P-glycoprotein.[177] Significant clinical interactions of St John's wort were demonstrated with the PI indinavir and with the NNRTI nevirapine. Therapeutic drug monitoring of protease inhibitors and NNRTIs is not routinely carried out, severe risks of interactions can only be assessed indirectly and delayed by surrogate markers (HIV viral load, CD4+ cell count) and finally, dose modification of protease inhibitors and NNRTIs would be very costly. Thus, concomitant use of St John's wort with these drugs should be contraindicated.

HIV nucleoside reverse transcriptase inhibitors are not metabolised by CYP enzymes or transported by P-glycoprotein.[177] Hence, such combinations with St John's wort should be able to be safely used.

4.2.3 Anticancer Drugs

Biotransformation and elimination of anti-neoplastic agents follow various routes and data regarding interactions with St John's wort are sparse. Thus, no general recommendations can be made for the concomitant use of St John's wort with the heterogeneous class of anticancer drugs. From two studies it appears to be clear that irinotecan and imatinib metabolism is significantly increased by St John's wort and these combinations should be contraindicated. P-glycoprotein induction is associated with drug resistance to anthracyclines, vinca alkaloids, podophyllotoxins and taxanes,[178] and potent CYP3A4 inducing antiepileptic drugs (e.g. carbamazepine, phenobarbital, phenytoin) have been demonstrated to reduce the effects of taxanes, vinca alkaloids, methotrexate, teniposide and camptothecin analogues.[179] One case of reduced efficacy of methotrexate in psoriasis was reported to a drug regulatory authority (table I). Against this background, decision making should take place on a case by case basis, and oncologists together with patients should consider the options and alternatives. Treatment with the above-mentioned classes of anticancer drugs that may be affected by induction of CYP3A4 and/or P-glycoprotein should be monitored more closely when St John's wort is the first choice antidepressant.

4.2.4 Oral Anticoagulants

Sufficient evidence from well documented case reports and clinical studies show that significant interactions of St John's wort with the anticoagulants warfarin and phenprocoumon may occur, resulting in both decreased as well as increased therapeutic activity, the latter probably more rarely. The underlying mechanism is ambiguous; although the primary route of metabolism of oral anticoagulants is oxidation by CYP2C9 and CYP2C19, not CYP3A4, the formation of precipitates may also play a role (see section 3.2.3). There is wide subjective variation in oral anticoagulant dose requirement and the list of drugs, foods and other factors that may affect their activity is prodigious and expanding.[180] Thus, therapeutic drug monitoring is routinely carried out, during recent years increasingly by the patients themselves, and drug effect should be assessed at closer intervals, when St John's wort is added, discontinued or the dosage is significantly changed.

4.2.5 Hormonal Contraceptives

To what extent St John's wort treatment affects efficacy of hormonal contraceptives cannot be determined unambiguously to date. The major route of inactivation of most progestogens is via oxidation by CYP3A4,[181] whereas this route of elimination accounts for only 30% of the dose of ethinylestradiol.[182,183] The occurrence of irregular bleeding during St John's wort co-administration seems to be verified by frequent reports to drug authorities and by significantly increased incidences in two interaction studies.[82,83] However, no hormonal signs of ovulation were observed (estradiol, progesterone, FSH, LH unchanged),[82,83] and vaginal endosonography revealed no differences in follicle maturation.[83] Bioavailability of the progestogen norethisterone and desogestrel appeared to be slightly decreased,[82,83] whereas ethinylestradiol pharmacokinetics remained by and large unaffected.[82-84] However, one study lacks important information and awaits full publication.[84] Another study underway, sponsored by the US National Center for Complementary and Alternative Medicine, may allow further insight into these processes.[184] Prelimi-

nary findings from this study appear to confirm results from the other studies.[185] In summary, a significant impact of St John's wort co-medication on contraceptive efficacy appears to be unlikely. On the other hand, three cases of unwanted pregnancy from the literature and another 17 cases from pharmacovigilance have been reported and cannot be ignored, although several of these reports may have been triggered by adverse publicity, which was very high during the year 2000.

Since impaired efficacy of hormonal contraceptives cannot be ruled out, women should be advised to additionally use mechanical methods of contraception or to stop St John's wort, and not to discontinue an oral contraceptive if irregular bleeding occurs.

4.2.6 Other Drugs

Clinical studies showing decreases of digoxin AUC by approximately 25% contrast with the lack of case reports, although drug monitoring is routinely established. This example may show that pharmacokinetic findings, even if statistically significant, may not necessarily translate into clinical relevance. This fact may also be true for several other drugs affected in interaction trials, like benzodiazepines (e.g. quazepam, midazolam), antibacterials (e.g. erythromycin), antidepressants (e.g. amitriptyline, nortriptyline) or antihistamines (e.g. fexofenadine), because these drugs are administered on the basis of therapeutic response and possess a rather broad therapeutic index. Furthermore, reduced drug concentrations or therapeutic responses of CYP3A4 substrates like HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin, but not pravastatin), methadone, thyroxine, and estrogens in hormone replacement therapy, which became apparent through a few case reports and an interaction trial (simvastatin), would not pose serious risks. More attentiveness is required regarding St John's wort co-medication with calcium channel antagonists like verapamil and nifedipine (interaction confirmed by clinical trials), since decreased drug effects may result in hypertension or cardiac arrhythmias. Nontheless, all of these potential interactions are controlled by drug effect monitoring and can be managed by dose modification.[76,101]

The antiepileptics carbamazepine, phenytoin and phenobarbital are probably not affected, as they are potent CYP3A4 inducers themselves and St John's wort has not been shown to further induce CYP3A4 which was already auto-induced by carbamazepine.[90]

4.2.7 General Considerations

Drugs with a narrow therapeutic index (e.g. oral anticoagulants, antiepileptic drugs, theophylline, digoxin, lithium) in general should be monitored more carefully when St John's wort is co-administered. It should also be noted that uncontrolled withdrawal of St John's wort after a suspected drug interaction has occurred, may result in an inverse increase in blood levels of the related drug accompanied by associated adverse reactions. Active questioning about the use of herbal remedies and St John's wort in particular should become a routine measure in patient interviews.

Topical and homeopathic preparations of St John's wort can be exempted from such questioning and advice, since corresponding systemic concentrations of St John's wort constituents are almost certainly below any clinical threshold level. Other St John's wort products should be regulated to comply with current pharmacopoeias to ensure minimal variability in composition.

St John's wort has had an excellent safety record over several decades with millions of users, particularly in mainland Europe. The observation that drug interactions have not been recognised until recently may be ascribed to the misperception of users as well as of healthcare professionals that 'natural' remedies are free from adverse effects. With regard to healthcare professionals this is somewhat surprising, since they are educated to appreciate that the complete absence of adverse effects is almost certainly associated with lack of efficacy. In fact, this is exactly what many doctors thought about herbal medicines and which is evidently not true for St John's wort. More effort must be made to inform and educate patients as well as healthcare professionals on a rational basis about herbal medicines and St John's wort in particular.

Early in the assessment process of St John's wort products by drug authorities in Ireland in January 2000, St John's wort was switched from an over-the-

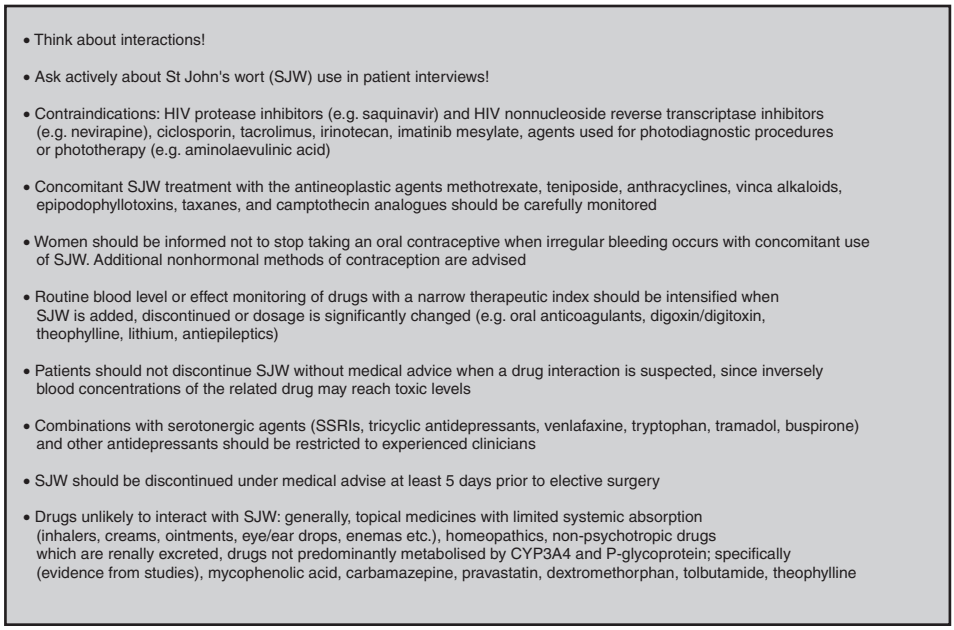

Fig. 1. Clinical implications and precautions regarding potential St John's wort drug interactions. **CYP** = cytochrome P450; **SSRIs** = selective serotonin reuptake inhibitors.

counter to a prescription-only medicine.[186] This action reflects the difficult regulatory situation that exists in many countries where St John's wort products are marketed as dietary supplements with no or little control over quality, safety and efficacy. A more pragmatic and reasoned approach occurred in Switzerland, Austria and Germany, where St John's wort products are regulated as drugs and labelling has been adapted step by step to reflect current knowledge. To ensure adequate information and advice, St John's wort products were made pharmacy-only medicines in June 2002 in Switzerland.[187] Monitored-release requirements that had been decreed by Swiss drug authorities in November 2001 were annulled in September 2003.[188] That such measures have been effective may be demonstrated by the continuously decreasing numbers of spontaneous reports since 2000.

Potential drug interactions with herbal medicines must be evaluated in the context of the increasing knowledge about the complex mechanisms of metabolism of xenobiotics. The daily confrontation with substances of mainly natural origin ingested with food means a biochemical chaos in our body that may result in various temporal changes of metabolic systems.[189,190] To mention only some more recent findings beside those already known: soy milk was found to decrease warfarin effect in a case report,[191] honey may be a potent intestinal and hepatic CYP3A4 inducer since it significantly increased clearance of oral carbamazepine and of oral and intravenous diltiazem in rabbits,[192,193] and finally, red wine decreases the bioavailability of ciclosporin in humans to a comparable extent as St John's wort.[194]

5. Conclusions

St John's wort administered as a monotherapy is a well tolerated treatment for depressive disorders. However, there is consistent evidence that clinically relevant drug interactions may occur when St John's wort is co-administered with other drugs, in particular with agents predominantly metabolised by CYP3A4 and P-glycoprotein at the same time. Therefore, some contraindications and precautions need to be considered and have been summarised in figure 1. Adequate information and education of patients and healthcare professionals about benefits and risks and reliably tested quality of St John's

wort products are recommended to ensure St John's wort can continue to be safely used. More research is required to further determine mechanisms and clinical implications of drug interactions with St John's wort.

Acknowledgements

The author thanks Rudolf Stoller of Swissmedic, Bern, Switzerland, and Leigh Henderson of the Medicines and Healthcare products Regulatory Agency, London, UK, for the provision of case report data and for discussing the drug regulatory agencies' view of the topic. Andreas Johne of the Institute of Clinical Pharmacology, Charité, Humboldt-University Berlin, Germany, and Harald Murck of Laxdale Ltd, Sterling, UK, reviewed the manuscript thoroughly and gave valuable hints for interpretation and discussion of the data. Richard W. Middleton of Medicherb UK Ltd, Marlow, UK, was a great help in proofreading and improving the linguistic quality of the manuscript and further made useful comments and suggestions for discussion of the topic.

Potential conflicts of interest/funding: from 1997–2001 the author was on the permanent staff of Lichtwer Pharma, Germany, a pharmaceutical company manufacturing St John's wort products. The author is occasionally paid by Lichtwer Pharma for medical consulting services in the field of phytotherapy.

Lichtwer Pharma supported this work by granting the author free access to literature database accounts.

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