

Interactions Between Herbal Medicines and Prescribed Drugs

An Updated Systematic Review

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Abstract

The concomitant use of herbal medicines and pharmacotherapy is wide spread. We have reviewed the literature to determine the possible interactions between seven popular herbal medicines (ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and conventional drugs. Literature searches were performed using MEDLINE, Cochrane Library and EMBASE and we identified 128 case reports or case series, and 80 clinical trials.

Clinical trials indicate that St John's wort (*Hypericum perforatum*), via cytochrome P450 (CYP) and/or P-glycoprotein induction, reduces the plasma concentrations (and/or increases the clearance) of alprazolam, amitriptyline, atorvastatin, chlorzoxazone, ciclosporin, debrisoquine, digoxin, erythromycin, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, ivabradine, mephenytoin, methadone, midazolam, nifedipine, omeprazole, oral contraceptives, quazepam, simvastatin, tacrolimus, talinolol, verapamil, voriconazole and warfarin. Case reports or case series suggest interactions of St John's wort with adrenergic vasopressors, anaesthetics, bupropion, buspirone, ciclosporin, eletriptan, loperamide, nefazodone, nevirapine, oral contraceptives, paroxetine, phenprocoumon, prednisone, sertraline, tacrolimus, theophylline, tibolone, tryptophan, venlafaxine and warfarin. Ginkgo (*Ginkgo biloba*) decreases the plasma concentrations of omeprazole, ritonavir and tolbutamide. Clinical cases indicate interactions of ginkgo with anti-epileptics, aspirin (acetylsalicylic acid), diuretics, ibuprofen, risperidone, rofecoxib, trazodone and warfarin. Ginseng (*Panax ginseng*) may interact with phenelzine and warfarin. Kava (*Piper methysticum*) increases the clearance of chlorzoxazone (a CYP2E1 substrate) and may interact with alprazolam, levodopa and paroxetine. Garlic (*Allium sativum*) interacts with chlorpropamide, fluindione, ritonavir and warfarin; it also reduces plasma concentrations of chlorzoxazone (a CYP2E1 probe). Echinacea might affect the clearance of caffeine (a CYP1A2 probe) and midazolam (a CYP3A4 probe). No interactions have been reported for saw palmetto (*Serenoa repens*).

Numerous interactions between herbal medicines and conventional drugs have been documented. While the significance of many interactions is uncertain, several interactions, particularly those with St John's wort, may have serious clinical consequences.

Plants have been used since the dawn of humanity for medical purposes and form the origin of much of modern pharmacotherapy. Plant extracts or derivatives are used in traditional healing systems such as Chinese herbal medicine, Indian (Ayurvedic) or Japanese (Kampo) medicine, and are practised in Western industrialized countries where their use is often integrated into conventional medicine.^[1-3] Herbal medicinal products have gained popularity in the last decade, and it is estimated they are now used by approximately 20% of the general population in the US^[4] and an even larger diversified proportion of patients. Their efficacy can be tested in clinical trials much like synthetic drugs, yet numerous methodological and logistical problems exist. The therapeutic value of several herbal medicines has been established; for many others, this is not the case, often because the research has not been done.^[1-4]

Many consumers believe that herbal medicines are natural and therefore safe, but this is a dangerous oversimplification. Some herbal medicines are associated with adverse effects, which include interactions with prescribed drugs.^[5-21] A recent survey found that 15% of patients receiving conventional pharmacotherapy also take herbal products and, among these, potential adverse herb-drug interactions were observed in 40% of patients.^[22] Approximately 38 million adults in the US (18.9% of the population) use herbs or other natural supplements, but only one-third tell their physician about this use.^[23] This lack of information, combined with the fact that herbal medicines are usually a mixture of many active ingredients, increases the likelihood of harm.

The aim of this article is to update our previous systematic review published in 2001.^[16] We examine the evidence pertaining to herb-drug

interactions involving seven best-selling herbal medicines, namely St John's wort (*Hypericum perforatum*), ginseng (*Panax ginseng*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*) echinacea (*Echinacea* spp.), saw palmetto (*Serenoa repens*) and kava (*Piper methysticum*).

1. Systematic Review

1.1 Methods

Systematic literature searches were conducted in the following databases: MEDLINE (via PubMed), EMBASE and Cochrane Library (all from their inception to January 2009). The search terms were the seven selected medicinal plants (English and Latin denominations) in combination with the terms 'drug interaction', 'adverse effects', 'side effects', 'adverse drug reaction', 'safety' and 'toxicity'. Recent reviews^[5-19] dealing with herb-drug interactions were also searched for further relevant information. Additional publications were identified by checking all reference lists. No language restrictions were imposed. All clinical reports (case reports, case series and clinical trials) of interactions were read, and relevant data were extracted by the first author into pre-defined tables and validated by the second author. Preclinical studies, including human *in vitro* experiments, animal data and dual publications were excluded.

1.2 Results

We found 128 cases of herb-drug interactions (108 for St John's wort, 8 for ginkgo, 6 for garlic, 3 for ginseng and 3 for kava) in 52 publications.^[24-75] No cases of interactions were found for echinacea and saw palmetto. In addition, 80 clinical trials were retrieved in 78 publications.^[76-152] One clinical trial was found to be published twice.^[128,153] In these clinical trials, St John's wort was evaluated for possible interaction with 38 conventional drugs, ginkgo with 20 drugs, garlic with 12 drugs, echinacea with 7 drugs, saw palmetto with 6 drugs, kava with 5 drugs and ginseng with 5 drugs. Key data from these publications are reported in table AI (case reports and case series) and table AII (clinical trials) [see Supplemental Digital Content 1,

<http://links.adisonline.com/DGZ/A4>] and summarized, more concisely, in table I.

2. Discussion

2.1 Echinacea

Echinacea preparations, widely used for the prevention and treatment of upper respiratory tract infections, are prepared from the roots and/or other parts of the plants belonging to the genus *Echinacea*, including *E. purpurea*, *E. angustifolia* and *E. pallida* (Fam Asteraceae). These multiple species have phytochemical similarities, but also have notable differences, particularly around the identity and concentration of alkylamides, chemical ingredients that can modulate cytochrome P450 (CYP) activity.^[154] As a monotherapy, echinacea appears to be safe, with little risk for the consumer.^[154] Conflicting results have been reported on the effect of echinacea on CYP activity. Gorski and colleagues^[76] found that echinacea (*E. purpurea* roots), 1600 mg/day for 8 days, reduced the oral clearance of CYP1A2 substrates (but not the oral clearance of substrates of CYP2C9 and CYP2D6), and selectively modulated the catalytic activity of CYP3A4 at hepatic and intestinal sites in healthy volunteers. However, two other trials found no effect of echinacea on CYP1A2, CYP2D6, CYP2E1 or CYP3A4.^[77,78] It is important to emphasize that these discrepancies could be due to the different species and part of plant used as well as to different dosages and duration of treatment (table AII [Supplemental Digital Content]). Moreover, echinacea does not affect the pharmacokinetics of digoxin, a probe substrate of P-glycoprotein.^[79] No case report of echinacea interactions has emerged. Although further studies into the interaction potential of this herbal medicine would be useful, the currently available evidence suggests that echinacea is unlikely to pose serious health threats for patients combining it with conventional drugs.

2.2 Garlic

Garlic (*Allium sativum* L., Fam Liliaceae) is used medicinally mainly for the treatment of hypercholesterolaemia and prevention of arteriosclerosis.

Table I. Summary of clinical herb-drug interactions (details can be found in tables AI and AII [Supplemental Digital Content])

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Echinacea				
Caffeine	Mixed results. Reduced (or no effect on the) clearance of caffeine	Inhibition of CYP1A2	Two pharmacokinetic trials	76,77
Chlorzoxazone	No effect on chlorzoxazone pharmacokinetics	None	One pharmacokinetic trial	77
Debrisoquine	No effect on debrisoquine pharmacokinetics	None	Two pharmacokinetic trials	77,78
Dextromethorphan	No effect on dextromethorphan pharmacokinetics	None	One pharmacokinetic trial	76
Digoxin	No effect on digoxin pharmacokinetics	None	One pharmacokinetic trial	79
Midazolam	Mixed results. Increased systemic clearance of midazolam associated with increased oral bioavailability of midazolam in one trial. No effect in another trial	Inhibition of intestinal CYP3A4 and induction of hepatic CYP3A	Two pharmacokinetic trials	76,77
Tolbutamide	No effect on tolbutamide pharmacokinetics	None	One pharmacokinetic trial	76
Garlic				
Alprazolam	No effect on alprazolam pharmacokinetics	None	One pharmacokinetic trial	80
Caffeine	No effect on caffeine pharmacokinetics	None	Two pharmacokinetic trials	81,82
Chlorzoxazone	Decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratios	Inhibition of CYP2E1	Two pharmacokinetic trials	81,82
Chlorpropamide	Hypoglycaemia	Additive effect on glucose levels	One case report	24
Ciclosporin	No effect on ciclosporin pharmacokinetics	None	One pharmacokinetic trial	83
Debrisoquine	No effect on debrisoquine urinary recovery ratios	None	Two pharmacokinetic trials	81,82
Dextromethorphan	No effect on dextromethorphan pharmacokinetics	None	One pharmacokinetic trial	80
Docetaxel	No significant effect on docetaxel disposition	None	One pharmacokinetic trial	84
Fluindione	Decreased fluindione INR	Not known	One case report	25
Midazolam	No effect on midazolam pharmacokinetics	None	Two pharmacokinetic trials	81,82
Paracetamol	Changes in paracetamol pharmacokinetic variables	Not known	One pharmacokinetic trial	85
Ritonavir	Severe gastrointestinal toxicity ^a	Not known	One case report	26
Saquinavir	Decreased saquinavir AUC and C _{max}	Not known	One pharmacokinetic trial	87
Warfarin	No effect on warfarin pharmacokinetics or pharmacodynamics ^b	None	Two clinical trials	88,89
Ginkgo				
Antiepileptics (valproic acid and phenytoin)	Fatal seizure with autopsy revealing subtherapeutic serum concentrations of both antiepileptics	Induction of CYP2C19	One case report	28
Aspirin (acetylsalicylic acid)	No additive effect on platelet aggregation ^c	None	One pharmacokinetic trial	90

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Table I. Contd

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Alprazolam	Slight decrease in alprazolam AUC	Weak inhibition of CYP3A4	One pharmacokinetic trial	91
Caffeine	No effect on caffeine pharmacokinetics	None	Two pharmacokinetic trials	81,82
Chlorzoxazone	No effect on chlorzoxazone pharmacokinetics	None	Two pharmacokinetic trials	81,82
Cilostazol	No enhancement of antiplatelet activity. However, ginkgo potentiated the bleeding time prolongation effect of cilostazol	Not known	One clinical trial	92
Clopidogrel	No enhancement of antiplatelet activity	None	One clinical trial	92
Debrisoquine	No effect on debrisoquine pharmacokinetics	None	Two pharmacokinetic trials	81,82
Dextromethorphan	No changes in urinary concentration of dextromethorphan metabolic ratios	None	One pharmacokinetic trial	91
Diclofenac	No effect on diclofenac pharmacokinetics	None	One pharmacokinetic trial	93
Digoxin	No effect on digoxin pharmacokinetics	None	One pharmacokinetic trial	94
Diuretic (thiazide)	Increased blood pressure	Not known	One case report	30
Fexofenadine	No effect on fexofenadine pharmacokinetics	None	One pharmacokinetic trial	95
Flubiprofen	No significant effect on flurbiprofen pharmacokinetics	None	One pharmacokinetic trial	96
Ibuprofen	Fatal intracerebral haemorrhage	Additive effects on coagulation mechanism	One case report	31
Lopinavir	No effect on lopinavir pharmacokinetics	None	One pharmacokinetic trial	95
Midazolam	Mixed results. No effect on midazolam pharmacokinetics in 2 trials, increased midazolam AUC in 1 trial, decreased midazolam AUC in another trial	None	Four pharmacokinetic trials	81,82,95,97
Nifedipine	No significant effect on nifedipine pharmacokinetics	None	One pharmacokinetic trial	98
Omeprazole	Reduction of plasma concentrations of omeprazole and omeprazole sulfone	Induction of CYP2C19	One pharmacokinetic trial	99
Phenazone (antipyrine)	No effect on phenazone $t_{1/2}$	None	One pharmacokinetic trial	100
Risperidone	Priapism	Not known	One case report	32
Ritonavir	Decreased ritonavir AUC and C_{max}	Not known	One pharmacokinetic trial	95
Rofecoxib	Bleeding	Additive effects on coagulation mechanism	One case report	33
Tolbutamide	Mixed results. No effect on tolbutamide pharmacokinetics in 1 trial; decreased tolbutamide AUC in another trial	Possible effect on CYP2C9	Two pharmacokinetic trials	93,97

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Table I. Contd

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Trazodone	Coma	Not known	One case report	34
Warfarin	No effect on INR and platelet aggregation in two trials ^d	None	Two clinical trials	101,102
Ginseng				
Caffeine	No effect on caffeine pharmacokinetics	None	Two pharmacokinetic trials	81,82
Chlorzoxazone	No effect on chlorzoxazone pharmacokinetics	None	Two pharmacokinetic trials	81,82
Debrisoquine	Weak or no effect on debrisoquine pharmacokinetics	Weak or no effect on CYP2D6	Two pharmacokinetic trials	81,82
Midazolam	No effect on midazolam pharmacokinetics	None	Two pharmacokinetic trials	81,82
Phenelzine	Insomnia, headache, tremulousness, irritability	Not known	Two case reports	36,37
Warfarin	No effect on the warfarin pharmacokinetics or pharmacodynamics ^e	None	Two clinical trials	103,104
Kava				
Alprazolam	Lethargic and disoriented state	Additive effect on GABA receptors	One case report	39
Caffeine	No changes in paraxanthine/caffeine serum ratios	None	One pharmacokinetic trial	105
Chlorzoxazone	Decreased 6-hydroxychlorzoxazone/ chlorzoxazone serum ratios	Inhibition of CYP2E1	One pharmacokinetic trial	105
Debrisoquine	No changes in debrisoquine urinary recovery ratio	None	Two clinical trials	78,105
Digoxin	No effect on digoxin pharmacokinetics	None	One pharmacokinetic trial	106
Levodopa	Reduced efficacy	Dopamine antagonism	One case report	40
Midazolam	No changes in 1-hydroxymidazolam/midazolam serum ratios	None	Two pharmacokinetic trials	106,107
Paroxetine	Lethargic state	Not known	One case report	42
Saw palmetto				
Alprazolam	No changes in alprazolam plasma concentration	None	One pharmacokinetic trial	108
Caffeine	No effect on caffeine pharmacokinetics	None	One pharmacokinetic trial	77
Chlorzoxazone	No effect on chlorzoxazone pharmacokinetics	None	One pharmacokinetic trial	77
Debrisoquine	No effect on debrisoquine pharmacokinetics	None	One pharmacokinetic trial	77
Dextromethorphan	No changes in dextromethorphan to dextrorphan metabolic ratios	None	One pharmacokinetic trial	108
Midazolam	No effect on midazolam pharmacokinetics	None	One pharmacokinetic trial	77
St John's wort				
Adrenergic vasopressors (ephedrine, phenylephrine)	Decreased responsiveness to vasopressors	Not known	One case report	42

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Table I. Contd

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Alprazolam	Decreased alprazolam AUC and $t_{1/2}$ ^f	Induction of CYP3A4; No effect on CYP3A4 after 3 d St John's wort or with extracts with low hyperforin content	One pharmacokinetic trial	110
Amitriptyline	Decreased amitriptyline AUC	Induction of CYP3A4 and/or induction of P-glycoprotein	One pharmacokinetic trial	112
Anaesthetics (fentanyl, propofol, sevoflurane in oxygen and nitrous oxide)	Delayed emergence	Not known	One case report	43
Atorvastatin	Reduced efficacy of atorvastatin	Induction of CYP3A4 and/or induction of P-glycoprotein	One pharmacokinetic trial	113
Bupropion	Orofacial dystonia	Additive effect on serotonin reuptake	One case report	44
Buspirone	Hypomanic episode, serotonin syndrome	Additive effect on serotonin reuptake	Two case reports	45,46
Carbamazepine	No changes in carbamazepine pharmacokinetics	None	One pharmacokinetic trial	114
Caffeine	Weak or no effect on caffeine pharmacokinetics ^g	None	Six pharmacokinetic trials	81,82,111, 115-117
Chlorzoxazone	Increase in hydroxylchlorzoxazone/chlorzoxazone ratio	Induction of CYP2E1	Two pharmacokinetic trials	81,82
Ciclosporin	Decreased plasma ciclosporin	Induction of CYP3A4 and/or P-glycoprotein induction	Multiple case reports, case series and two clinical trials	57-61, 118,119
Debrisoquine	Weak or no effect on debrisoquine urinary recovery ratios	Weak or no induction of CYP2D6	Three pharmacokinetic trials	78,81,82
Dextromethorphan	No effect on dextromethorphan pharmacokinetics	None	Five clinical trials	109,110,115, 117,120
Digoxin	Decreased plasma digoxin concentration (in 4 of 5 studies)	Induction of P-glycoprotein	Five pharmacokinetic studies	79,111, 121-123
Eletriptan	Serotonin syndrome	Additive effect on serotonin signalling	One case report	62
Erythromycin	Increased metabolism of erythromycin	Induction of CYP3A4	One pharmacokinetic study	123

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Table I. Contd

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Fexofenadine	Decreased plasma concentration of fexofenadine ^h	Induction of P-glycoprotein	Two pharmacokinetic trials	118,125
Gliclazide	Decreased gliclazide AUC, $t_{1/2}$ and apparent clearance	Not known	One pharmacokinetic trial	126
Imatinib	Decreased imatinib AUC, $t_{1/2}$ and C_{max}	Induction of CYP3A4	Two pharmacokinetic trials	127,128
Indinavir	Decreased indinavir AUC	Induction of CYP3A4	One pharmacokinetic trial	129
Irinotecan	Decreased plasma concentrations of SN-38 (the active metabolite of irinotecan)	Induction of CYP3A4	One pharmacokinetic trial	130
Ivabradine	Decreased ivabradine AUC and C_{max}	Induction of CYP3A4	One pharmacokinetic trial	131
Loperamide	Acute delirium	Not known	One case report	63
Mephenytoin	Increased urinary excretion of mephenytoin metabolites	Induction of CYP2C19	One pharmacokinetic trial	116
Methadone	Decreased methadone plasma concentration	Induction of CYP3A4 and/or P-glycoprotein	One clinical trial	132
Mycophenolic acid	No changes in mycophenolic acid pharmacokinetics	None	One pharmacokinetic trial	133
Midazolam	Decreased midazolam AUC ⁱ	Induction of intestinal (and possibly hepatic) CYP3A	Seven pharmacokinetic trials	81,82,115,118, 134,135,137
Nefazodone	Serotonin syndrome	Additive effect on serotonin reuptake	One case report	64
Nevirapine	Decreased nevirapine plasma concentration in 2 subjects ^j	Induction of CYP3A4	Two cases in one publication	65
Nifedipine	Decreased nifedipine AUC	Induction of CYP3A4	One pharmacokinetic trial	139
Omeprazole	Decreased omeprazole AUC and C_{max}	Induction of CYP2C19	One pharmacokinetic trial	140
Oral contraceptive	Changes in the pharmacokinetics of oral contraceptive resulting in reduced efficacy. Increased breakthrough bleeding ^k	Induction of CYP3A4	Three pharmacokinetic trials, case series and a case report	47,66,67, 134,141,142
Paroxetine	Serotonin syndrome	Additive effect on serotonin reuptake	One case report	68
Phenprocoumon	Decreased phenprocoumon AUC and pharmacological effect	CYP induction	One pharmacokinetic trial and one case report	47,144
Pravastatin	No effect on plasma pravastatin concentrations	None	One pharmacokinetic trial	145
Prednisone	No changes in prednisone pharmacokinetics ^l	None	One pharmacokinetic trial	146
Quazepam	Decreased quazepam C_{max} and AUC	Induction of CYP3A4	One pharmacokinetic trial	147
Sertraline	Serotonin syndrome	Additive effect on serotonin reuptake	Five cases in two publications	64,70

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Table I. Contd

Prescribed drug	Clinical result of interaction	Possible mechanism	Source of evidence	References
Simvastatin	Decreased plasma simvastatin	Induction of CYP3A4 and/or P-glycoprotein	One pharmacokinetic trial	145
Tacrolimus	Decreased tacrolimus AUC	Induction of CYP3A4 and/or P-glycoprotein	Two pharmacokinetic trials and one case report	71,133,148
Talinolol	Decreased talinolol AUC	Induction of intestinal P-glycoprotein	One pharmacokinetic trial	149
Theophylline	No significant changes in theophylline pharmacokinetics ^m	None	One pharmacokinetic trial	150
Tibolone	Acute hepatitis	Not known	One case report	73
Tolbutamide	Weak or no effect on tolbutamide pharmacokinetics	Weak or no effect on CYP2C9	Two pharmacokinetic trials	111,115
Tryptophan	Serotonin syndrome	Additive effect on serotonin signalling	One case report	74
Venlafaxine	Serotonin syndrome	Additive effect on serotonin reuptake	One case report	75
Verapamil	Decreased verapamil AUC	Induction of intestinal CYP3A4	One pharmacokinetic trial	151
Voriconazole	Increased AUC after 10 h, decreased AUC after 14 d St John's wort	CYP2C19 modulation	One pharmacokinetic trial	152
Warfarin	Increased warfarin clearance and decreased INR	Induction of CYP3A4 and possibly other CYP isoforms	One clinical trial and seven cases in one publication	66,103

a A clinical trial showed no effect of garlic on ritonavir pharmacokinetics.^[86]

b A case of increased INR has been described.^[27]

c A case of spontaneous hyphaema has been reported.^[29]

d A case of intracerebral haemorrhage has been reported.^[35]

e A case of decreased INR has been reported.^[38]

f Weak or no effect on alprazolam pharmacokinetics after short periods (3 days)^[109] or with extracts with low hyperforin content.^[111]

g One trial reported increased excretion of caffeine in females only.^[111]

h Increased fexofenadine maximum plasma concentration after 1 day of St John's wort.^[124]

i Weak effect on midazolam pharmacokinetics in two trials in which extracts with low hyperforin content were used.^[135,136]

j No effect on nevirapine $t_{1/2}$ in one trial in which a St John's wort tea was used.^[138]

k No effect was observed in a trial in which an extract with low hyperforin content was used.^[143]

l One case of manic episode has been reported.^[69]

m A case of decreased theophylline concentrations has been reported.^[72]

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **CYP** = cytochrome P450; **INR** = international normalized ratio; **t_{1/2}** = elimination half-life.

Case reports have suggested that garlic might influence platelet function and blood coagulation, leading to a risk of bleeding.^[155] The international normalized ratio (INR) of two patients previously stabilized on warfarin was reported to have changed after garlic intake in a single publication.^[27] However, two trials have reported that garlic (enteric-coated tablets or aged garlic extract) did not alter the pharmacokinetics or pharmacodynamics of warfarin and that garlic poses no serious haemorrhagic risk for adequately monitored patients receiving warfarin.^[88,89] Surprisingly, garlic has been suggested to decrease the INR of the anticoagulant fluindione in an 82-year-old man.^[25] We are not aware of a rational explanation for such an interaction.

Two clinical trials implied that garlic oil may selectively inhibit CYP2E1, as revealed by the decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratios, but not other CYP isoforms (such as CYP1A2, CYP3A4 or CYP2D6).^[81,82] No effect on CYP3A4 has been reported for garlic powder.^[80,84]

Garlic might cause interactions in patients receiving antiretroviral therapy.^[155] A significant decline in the plasma concentrations of the protease inhibitor saquinavir was observed in healthy volunteers after administration of garlic for 3 weeks.^[87] Although it has been hypothesized that changes in saquinavir bioavailability could be secondary to the induction of intestinal CYP3A4, experimental evidence in humans did not confirm this^[81,84] (see previous paragraph). Saquinavir is also a P-glycoprotein substrate, which, based on *in vitro* studies, is unlikely to be induced by garlic or garlic components.^[155,156] Another trial showed that acute dosing of garlic over 4 days did not significantly alter the single-dose pharmacokinetics of the protease inhibitor ritonavir (a CYP3A4 and P-glycoprotein substrate);^[86] the reason for the discrepancies is presently unclear. Zhou and colleagues^[14] suggested that a longer duration of garlic therapy may be required to observe a significant decrease in ritonavir plasma concentrations. One report described the case of two HIV-positive individuals who developed severe gastrointestinal toxicity from ritonavir after ingesting garlic supplements.^[26] Symptoms recurred after re-challenge

with low-dose ritonavir in the absence of garlic intake, suggesting that an elevated ritonavir concentration was not the cause. Thus, ritonavir could inhibit the metabolism of the active ingredients of garlic (pharmacokinetic interaction) or it could potentiate the toxic effect of garlic on the intestinal tract (pharmacodynamic interaction).^[157]

Other conventional drugs that might interact with garlic include the antidiabetic chlorpropamide and the analgesic drug paracetamol (acetaminophen). A fall in glucose levels has been reported in a 40-year-old diabetic woman taking chlorpropamide and a curry containing garlic and karela.^[24] This effect might be due to an additive effect since both garlic and karela possess hypoglycaemic effects. However, the report contained inadequate information to assess the likelihood of a causal relationship.^[158] A clinical trial suggested that garlic changes some pharmacokinetic variables of paracetamol.^[85] However, it is unlikely that these pharmacokinetic changes are of major clinical significance. Finally, a clinical trial suggested chewed raw garlic significantly reduced cholesterol and triglyceride levels, but did not significantly decrease ciclosporin serum concentrations in renal transplant recipients.^[83]

In summary, caution is advised if garlic is taken concomitantly with CYP2E1 substrates or with antiretroviral drugs such as ritonavir and saquinavir. The possibility that garlic may cause over-anticoagulation if coadministered with anticoagulant drugs has been not confirmed by clinical trials.^[88,89]

2.3 Ginkgo

Ginkgo (*Ginkgo biloba* leaves) is mainly used for memory deficits, tinnitus and peripheral vascular disease. Its constituents (ginkgolide, bilobalides and others) have antiplatelet activity and are platelet-activating factor (PAF) receptor antagonists;^[159] accordingly, ginkgo has been suggested to cause bleeding postoperatively.^[160,161] Case reports implied that patients taking drugs with effects on platelet function and/or coagulation, such as warfarin or the NSAIDs aspirin (acetylsalicylic acid), ibuprofen or rofecoxib, experienced bleeding after self-prescribing ginkgo

at recommended doses.^[29,31,33] Adverse events were particularly severe for aspirin (spontaneous hyphaema),^[29] warfarin (intracerebral haemorrhage)^[35] and ibuprofen (comatose state with an intracerebral mass bleeding of which the patient died).^[31] However, recent trials did not confirm these effects.^[90,92,93,96] In one trial,^[92] ginkgo potentiated the effect of cilostazol on bleeding time, but no significant correlation between the prolongation of bleeding time and the inhibition of platelet aggregation was found. A systematic review of case reports concluded that “the causality between ginkgo intake and bleeding is unlikely”.^[162] A systematic review of eight randomized controlled trials concluded that the “available evidence does not demonstrate that extract of *G. biloba* causes significant changes in blood coagulation parameters”.^[163]

The effect of ginkgo on CYP enzymes has been evaluated in clinical trials using, as probe drugs, alprazolam, midazolam, nifedipine (CYP3A4), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), tolbutamide, diclofenac, flurbiprofen (CYP2C9) and omeprazole (CYP2C19).^[81,82,91,93,95,97-99] Although not all results were uniform, particularly not for the CYP3A4 isoform, an effect on CYP enzymes by ginkgo seems unlikely. A possible exception is the CYP2C19 isoform. A 12-day ginkgo treatment induced omeprazole hydroxylation in a CYP2C19 genotype-dependent manner and concurrently reduced the renal clearance of 5-hydroxyomeprazole, suggesting CYP2C19 induction.^[99] Conversely, two trials suggested that ginkgo does not affect the pharmacokinetics of fexofenadine or digoxin, two P-glycoprotein substrates.^[94,95]

The effect of ginkgo on CYP2C19 could explain, at least in part, a case of fatal seizures as a result of potential herb-drug interactions with ginkgo in a 55-year-old male taking the anti-epileptic drugs valproic acid and phenytoin.^[28] Both antiepileptics are metabolized by a number of CYP isoforms, including CYP2C19. At autopsy, the patient had subtherapeutic serum concentrations of both antiepileptics. Concomitant with his prescribed medications, the decedent was also self-medicating with a cornucopia of herbal supplements and nutraceuticals, prominent

among which was ginkgo. Although the fluctuations in the concentrations of valproic acid and phenytoin could not definitively be attributed to herb-drug interactions, caution is suggested in the use of ginkgo in patients with convulsive disorders.^[28]

A possible case of priapism due to the concurrent use of risperidone and ginkgo has been reported.^[32] A 26-year-old man presented with a painful erection lasting for 4 hours. Two weeks before admission, he began taking ginkgo for tinnitus. He denied any adverse effects resulting from antipsychotic therapies or the use of other drugs.^[32] Because both ginkgo and risperidone have vessel-dilating properties, an additive or synergistic effect might explain such an interaction.

Another drug that might interact with ginkgo is the antidepressant trazodone.^[34] An 80-year-old woman with Alzheimer's disease fell into a coma after taking a low dose of trazodone with ginkgo; the causality was classified as ‘possible’.^[158]

In summary, the notion that the combination of ginkgo and anticoagulant or antiplatelet drugs might represent a serious health risk is based on several case reports but not supported by clinical trials. Ginkgo should be not taken concomitantly with CYP2C19 substrates, while the effect of ginkgo on CYP3A4 requires additional study.

2.4 Ginseng (Asian Ginseng)

Asian (or Korean) Ginseng (roots of *Panax ginseng*) is marketed for a wide range of indications, which include erectile dysfunction, cancer prevention, enhanced physical function and improved cognitive functions.^[164] This discussion relates to Asian ginseng extracts, which are generally standardized to ginsenosides. They should not be confused with American ginseng (roots of *Panax quinquefolium*), the preparations of which are generally standardized to polysaccharides or with Siberian ginseng products (roots of *Eleutherococcus senticosus*), which are characterized by the presence of a heterogenous group of compounds named eleutherosides.

Clinical studies have shown that ginseng has no effect on a number of CYP isoforms, including CYP3A4, CYP1A2, CYP2E1 and CYP2D6.^[81,82]

However, a slight CYP2D6 inhibition has been described in the elderly.^[81] Although ginseng extracts have been shown to inhibit platelet aggregation,^[164] decreased INR in a patient taking the anticoagulant warfarin has been reported.^[38] Because the patient took several other drugs concomitantly, causality is uncertain. Furthermore, clinical studies have not confirmed that ginseng affects platelet function,^[165] or alters the pharmacokinetics and pharmacodynamics of warfarin.^[103,104] It is worthy of note that American ginseng has been shown to reduce the anticoagulant effect of warfarin.^[166]

A patient experienced insomnia, headache, tremulousness and mania after coadministration of ginseng with the antidepressant drug phenelzine;^[36] in this case, causality is likely because inadvertent re-challenge resulted in similar symptoms.^[37,167]

In summary, available clinical evidence suggests that the potential for ginseng-drug interactions is low. Nevertheless, interactions with the antidepressant phenelzine should be considered.

2.5 Kava

Despite about 80 reported cases of apparent hepatotoxicity, kava (*Piper methysticum* roots and rhizome) continues to be a popular herbal anxiolytic.^[1] Clinical studies have shown that kava inhibits CYP2E1, but not other CYP isoforms, such as CYP3A4, CYP2D6 or CYP1A2, or P-glycoprotein.^[78,105-107]

Single case reports have suggested interactions of kava with the antiparkinsonian drug levodopa, resulting in reduced efficacy,^[40] and with the benzodiazepine alprazolam, causing a semi-comatose state.^[39] These effects might have a pharmacodynamic basis, since kava antagonizes dopamine effects, which may explain the reduced efficacy of levodopa, and kava may also interact, like benzodiazepines, with GABA receptors.^[3]

A lethargic state in a 44-year-old male has been reported.^[41] He had mild left-right confusion, difficulty repeating phrases and diffuse muscular weakness with no other focal findings. Two months previously, the patient had begun taking kava and valerian root along with parox-

etine for depression. With each hospital admission, he stopped the herbal remedies and his symptoms subsided. They rebounded when he started taking them again.^[41]

In summary, kava should be not taken concomitantly with CYP2E1 substrates, and possibly not with dopaminergic drugs or benzodiazepines.

2.6 Saw Palmetto

Extracts obtained from the ripe, dried fruit of saw palmetto (*Serenoa repens* Bartram) are widely used for the treatment of benign prostatic hyperplasia stages I and II. Despite careful assessments, no clinical evidence for serious toxicity with saw palmetto has been clinically observed.^[168,169] There is also no evidence for herb-drug interactions of any kind. Using alprazolam, midazolam, caffeine, chlorzoxazone, debrisoquine and dextromethorphan as probe substrates, two clinical studies found that saw palmetto had no significant effects on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 in healthy volunteers.^[77,108] Overall, saw palmetto seems to pose no risk for drug interactions in humans.

2.7 St John's Wort

St John's wort (*Hypericum perforatum*) is an effective herbal medicine for mild, moderate and major depression.^[170,171] As a monotherapy, St John's wort has an encouraging safety profile.^[172,173] However, a number of clinical reports indicate the possibility of important interactions, mainly pharmacokinetic interactions, with prescribed drugs. Such interactions are likely to be due to the ability of St John's wort to induce CYP enzymes and/or intestinal P-glycoprotein.^[173-179]

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 have consistently shown that St John's wort induces CYP3A4, CYP2E1 and CYP2C19, with no effect on CYP1A2, CYP2D6 or CYP2C9.^[78,81,82,109-111,115-118,120,125,134,137,140] The *in vivo* CYP3A activity returns progressively to

the basal level approximately 1 week after cessation of St John's wort.^[137] Similarly, St John's wort has been shown to lower plasma concentrations of well known P-glycoprotein substrates, including digoxin,^[79,121-123] fexofenadine^[118,125] and talinolol.^[149] The effect on probe substrates was associated with increased multidrug resistance 1 (MDR1) mRNA as well as P-glycoprotein levels in the human intestinal mucosa.^[149] Interestingly, the effect of St John's wort on P-glycoprotein or CYP enzymes was observed after long-term treatment (generally 14 days), with studies reporting no effect (or even stimulating effects) following acute St John's wort administration.^[109,124,152] The relative contributions of CYP3A4 and P-glycoprotein to drug clearance has been assessed in 21 healthy volunteers using midazolam, fexofenadine and ciclosporin (which is considered to reflect both CYP3A4 and P-glycoprotein activity) as probe drugs. It was found that the effect of St John's wort on CYP3A4 and P-glycoprotein was comparable.^[118] Finally, clinical evidence suggests that 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.^[111,119,135,136,138,143]

St John's wort has been shown to clinically interact with a number of drugs, including immunosuppressants, contraceptives, cardiovascular, anti-retroviral and anticancer drugs, drugs acting on the CNS (such as antidepressants, anxiolytics, anti-epileptics and muscle relaxing agents) gastrointestinal tract and respiratory system, hypoglycaemics, anti-inflammatories, antimicrobials and anti-migraine medicines. These interactions, summarized in tables AI, AII [Supplemental Digital Content] and table I, are detailed below.

2.7.1 Immunosuppressants

After transplantation, there may be an increased incidence of depressive episodes. St John's wort has been shown to interact with the immunosuppressants ciclosporin and tacrolimus. Multiple case reports and case series of interactions between St John's wort and ciclosporin have been reported,^[47-61] making this interaction the most well documented. The common clinical features of

these reports are that heart, renal or liver transplant patients stabilized on ciclosporin showed decreased plasma concentrations (associated, in some cases, with acute rejection episodes) after taking St John's wort at therapeutic dosages.^[180] The clinical picture improved in most patients following discontinuation of the herbal extract. The St John's wort-ciclosporin interaction has been confirmed by two clinical trials.^[118,119] Another immunosuppressant that might interact with St John's wort is tacrolimus, as illustrated in a case report^[71] and in two clinical trials.^[133,148] Notably, Mai et al.^[133] found that St John's wort decreased the blood concentrations of tacrolimus (a CYP3A4 and P-glycoprotein substrate), but not of mycophenolic acid (mainly glucuronidated by uridine diphosphate glucuronosyl transferase [UGT]1A9 and 2B7) in ten stable renal transplant patients.

Although St John's wort has been shown not to alter the pharmacokinetics of prednisone,^[146] a case of mania due to co-administration of St John's wort with prednisone has been reported.^[69] Both St John's wort and prednisone may cause mania when administered alone. The patient was abusing cocaine and alcohol; causality is therefore not certain.

2.7.2 Hormonal Therapy

Clinical evidence suggests that St John's wort may affect hormonal contraception. Numerous cases of women becoming pregnant whilst using oral contraceptives and St John's wort have been reported by authorities in the UK (seven cases), Germany (four cases) and Sweden (two cases).^[181] A further case report of a 36-year-old woman who became pregnant after self-prescribing a combined oral contraceptive (ethinylestradiol/dienogest) has been published.^[67] The clearance of hormones such as ethinylestradiol, norethindrone and ketodesogestrel has been shown to be increased by St John's wort in three clinical trials;^[134,141,142] a fourth clinical trial suggested that a St John's wort extract with a low hyperforin content does not change the plasma concentrations of oral contraceptives.^[143] Changes in the plasma concentrations of ethinylestradiol might also explain several reports of breakthrough bleeding.^[47,66,134,141,142]

A patient taking tibolone (a synthetic steroid used for menopausal symptoms) for 2 years developed a mixed-type liver injury with prolonged cholestasis and features of the vanishing bile duct syndrome following 10 weeks treatment with St John's wort.^[73] In the absence of evidence for alternative explanations, an interaction between St John's wort and tibolone was suspected as the likely cause of the liver damage.

2.7.3 Cardiovascular Drugs

Interactions between St John's wort and cardiovascular drugs, including coumarin anticoagulants, cardiotonics, antiarrhythmic, antihypertensive and antihyperlipidaemic drugs could have serious consequences.^[182] Several cases have been reported of reduced anticoagulation of warfarin^[66] and phenprocoumon (a coumarin anticoagulant chemically related to warfarin)^[47] after administration of St John's wort. It is likely that St John's wort reduces plasma warfarin concentrations through induction of CYP3A4 and possibly other CYP isoforms because warfarin, which exists as a racemic mixture of R- and S-enantiomers, is metabolized by CYP1A1 and CYP3A4 (R-warfarin) and CYP2C9 (S-warfarin). Such interactions have been confirmed in clinical trials showing decreased plasma concentrations of warfarin^[103] and phenprocoumon.^[144]

Other pharmacokinetic interactions, due to CYP or P-glycoprotein induction, confirmed in clinical studies, include decreased plasma concentrations of the cardiotonic digoxin (P-glycoprotein substrate),^[79,121,122] the antiarrhythmic ivabradine (extensively metabolized by hepatic and intestinal CYP3A4),^[131] the calcium channel antagonists nifedipine and verapamil (both metabolized by CYP3A4),^[139,151] the β -adrenoceptor antagonist talinolol (a probe of P-glycoprotein),^[149] and the antihyperlipidaemic drugs simvastatin^[145] and atorvastatin^[113] (CYP and P-glycoprotein substrates) but not pravastatin (non-CYP, non-P-glycoprotein substrate).^[145]

2.7.4 Antiretrovirals Drugs

Several herbal medicines, including St John's wort, have been shown to interact with anti-

retroviral drugs, which can lead to drug failure.^[183] An open-label trial showed a large reduction in the plasma concentration of the protease inhibitor indinavir, a CYP3A4 substrate, in eight healthy volunteers taking St John's wort.^[129] A patient experienced an increase in HIV RNA viral load following the use of St John's wort concomitantly with indinavir and lamivudine.^[10] Increased oral clearance of nevirapine (a non-nucleoside reverse transcriptase inhibitor) following St John's wort co-administration has been demonstrated in five HIV patients.^[65] Nevirapine metabolism is catalyzed by CYP3A4 and CYP2D6.^[184]

2.7.5 Anticancer Drugs

Considering the narrow therapeutic window of drugs used in cancer therapy, herb-anticancer drug interactions are of particular clinical relevance.^[185] Two trials performed in healthy volunteers have shown decreased plasma concentrations of imatinib (a potent inhibitor of the Bcr-Abl and c-kit tyrosine kinases that promote tumour cell proliferation) after administration of St John's wort.^[127,128] Imatinib is mainly metabolized by CYP3A4 and transported by P-glycoprotein, both induced by St John's wort. Another trial showed that St John's wort decreased plasma concentrations of SN-38, the active metabolite of irinotecan (a known substrate for CYP3A4 employed in the treatment of colorectal cancer).^[130]

2.7.6 Drugs Acting on the CNS

St John's wort self-medication in people with mental health problems, including anxiety and depression, is well documented.^[186] Consistently, multiple interactions have been documented with drugs acting on the CNS.

Because of its ability to induce CYP3A4, St John's wort decreases plasma concentrations of the benzodiazepines alprazolam,^[110] midazolam^[81,82,115,118,134,135,137] and quazepam.^[147] Some studies found that the effects of St John's wort were considerably less after intravenous administration than after oral administration.^[115,118] This suggests that the primary site of action of St John's wort is intestinal, rather than

hepatic, CYP3A4. Another anxiolytic drug that may interact with St John's wort is buspirone. A possible serotonin syndrome after combination of buspirone (a serotonin 5-HT_{1A} agonist) and St John's wort has been reported.^[46] In addition, a female patient experienced hypomania after adding St John's wort and ginkgo to her regimen of buspirone and fluoxetine.^[45] Such interactions can be due to increased serotonin signalling since St John's wort is known to inhibit serotonin reuptake in several brain areas.^[173]

Depressed patients often self-prescribe St John's wort. Multiple case reports have indicated that St John's wort interacts with serotonin reuptake inhibitors (e.g. the antidepressants paroxetine, sertraline, venlafaxine and nefazodone), resulting in symptoms of a central serotonin syndrome.^[64,68,75,187] These effects could be the result of an additive effect on serotonin reuptake (or serotonin receptors). Such a pharmacodynamic mechanism would also explain the occurrence of mania in a 28-year-old man taking both St John's wort and sertraline.^[70] On the other hand, a pharmacokinetic interaction, revealed by a clinical trial, has been reported with the antidepressant amitriptyline, resulting in reduced plasma concentrations of the synthetic antidepressant.^[112]

Clinical trials showed that St John's wort decreased plasma concentrations of the anti-epileptic agent mephenytoin,^[116] which is primarily metabolized by CYP2C9 and CYP2C19. In contrast, a trial found that St John's wort did not alter the pharmacokinetics of carbamazepine,^[114] which is metabolized by CYP3A4; conversely, treatment with carbamazepine for 7 days resulted in a significant decrease in the plasma concentration of pseudohypericin, one of the active ingredients of St John's wort preparations.^[188] This represents an unusual case of interaction in which a synthetic drug affects the pharmacokinetics of an active ingredient of an herbal extract.

Drugs used to relieve symptoms of withdrawal from drug dependence have been shown to interact with St John's wort. Thus, the herb has been demonstrated to lower plasma concentrations of methadone (mainly metabolized by CYP3A4) in four heroin-dependent patients.^[132]

Two of these patients reported symptoms suggestive of withdrawal syndrome. Also, orofacial dystonia in a 58-year-old woman following therapy with St John's wort and bupropion (a drug used to stop smoking) has been reported.^[44] An additive effect on serotonin reuptake inhibition is believed to be the cause. Finally, a case of serotonin syndrome resulting from coadministration of St John's wort and tryptophan in which a 19-year-old man used these agents to 'detox' himself from ecstasy has been reported.^[74] 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 St John's wort.^[74] Tryptophan is the precursor of serotonin and, hence, might increase its brain levels.

Interactions between prescribed medications and anaesthetic drugs are often encountered during the induction and maintenance of general and regional anaesthesia. Patients are therefore usually asked to discontinue herbal medicines before surgery.^[189] Delayed emergence from anaesthesia has been reported in a 21-year-old woman.^[43] On recovery, she denied taking any benzodiazepine, barbiturate, opioid or cannabinoid drugs preoperatively, but she admitted taking St John's wort and even increased the recommended dose because of a perceived lack of antidepressant effects. The mechanism of such an interaction needs further investigation. Cardiovascular collapse during anaesthesia has been reported in a 23-year-old woman.^[42] The patient was found to be only weakly responsive to adrenergic vasopressors. The mechanism of such an interaction is unknown, although the authors speculated that St John's wort might theoretically reduce the expression of adrenergic receptors.

Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain or discomfort. Two clinical trials found increases in hydroxylchlorzoxazone-chlorzoxazone serum ratios after taking St John's wort, which is suggestive of CYP2E1 induction. The effect was found to be more pronounced in young subjects.^[81,82]

2.7.7 Drugs Acting on the Respiratory System

Decreased plasma concentrations of theophylline (metabolized mainly by CYP1A2, CYP2E1 and CYP3A4) has been reported in an asthmatic patient taking St John's wort.^[72] This interaction was not confirmed by a clinical trial which showed no effects of St John's wort on the pharmacokinetics of theophylline in healthy volunteers.^[150] In contrast, it is well documented in clinical trials that St John's wort reduces plasma concentrations of fexofenadine, a long-acting antihistaminic drug, which is experimentally used as a P-glycoprotein probe.^[118,125] Finally, multiple clinical trials^[109,110,115,117,120] have shown that St John's wort does not affect the pharmacokinetics of the antitussive drug dextromethorphan, a CYP2D6 substrate.

2.7.8 Hypoglycaemic Drugs

Studies on the potential of St John's wort to interact with hypoglycaemic agents have been published. Two clinical trials showed that St John's wort did not alter the pharmacokinetics of tolbutamide, a CYP2C9 substrate.^[111,115] In contrast, St John's wort significantly alters the pharmacokinetics of gliclazide.^[126] However, no significant differences according to CYP2C9 genotype were noted. Thus, St John's wort may increase the clearance of gliclazide independent of CYP2C9 genotype.^[126]

2.7.9 Antimicrobials

The ¹⁴C erythromycin breath test, performed by administering a trace amount of ¹⁴C-labelled erythromycin and evaluating the amount of exhaled ¹⁴CO₂, is commonly used for evaluating CYP3A4 activity. Consistent with the ability of St John's wort to induce CYP3A4, a 40% increase in the activity of hepatic CYP3A4 has been observed after administration of St John's wort.^[123] In a controlled trial, co-administration of St John's wort was found to cause a short-term, but clinically irrelevant increase, followed by a prolonged extensive reduction in plasma voriconazole (an antifungal drug and CYP2C19 substrate) concentrations.^[152] These findings support the concept that enzymatic induction

occurs mainly after long-term administration of St John's wort.

2.7.10 Antimigraine Drugs

Serotonin syndrome and rhabdomyolysis induced by concomitant use of eletriptan, fluoxetine and St John's wort has been reported in a 28-year-old woman.^[62] The authors believe that St John's wort and fluoxetine predisposed the patient to develop serotonin syndrome, which was precipitated by subsequent use of eletriptan (an antimigraine drug that binds to 5-HT_{1B} and 5-HT_{1D} receptors).

2.7.11 Drugs Acting on the Gastrointestinal Tract

The proton pump inhibitor omeprazole is used as a probe to investigate the effect of drugs on CYP2C19. Wang and colleagues^[140] found that two weeks of St John's wort administration induced both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole and considerably decreased the plasma concentrations of omeprazole. A brief episode of acute delirium, possibly after the intake of St John's wort, valerian and the antidiarrhoeal drug loperamide has been reported.^[63] The mechanism of such an interaction is presently unclear.

2.7.12 Summary of St John's Wort Interactions

St John's wort may cause both pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions (lowering of plasma concentrations) arise when St John's wort is combined with drugs that are substrates of CYP3A4, CYP2E1 and CYP2C19, and/or P-glycoprotein. Among these, interaction with ciclosporin or antiretrovirals drugs may have serious clinical consequences. Hyperforin is the ingredient of St John's wort responsible for P-glycoprotein and CYP induction. Pharmacodynamic interactions may occur when St John's wort is combined with drugs that enhance serotonin signalling in the brain. For example, St John's wort has been shown to cause serotonin syndrome when combined with serotonin reuptake inhibitors and serotonin receptor agonists.

3. Limitations

Our update shows that, as a result of intensive research efforts, we are currently fast filling the considerable gaps in our knowledge about herb-drug interactions (table I). The literature has now grown to such an extent that future updates on this subject might have to focus on more specific aspects, i.e. interactions related to one single herbal medicine.

This review has several important limitations. Even though our search strategy was thorough, we cannot be sure that we have located all relevant articles. Crucially, much of the evidence discussed above is based on case reports. Many of these publications are of poor quality and omit potentially important details. Even the most detailed case report will never be able to establish cause and effect. Therefore, it is clear that we need more experimental studies if we want to advance this field of knowledge.

The study of herb-drug interactions is further hindered by the nature of herbal medicines. Invariably (and by definition) these are not drugs with only one pharmacologically active constituent. Typically, we are dealing with complex mixtures of dozens of potentially active principles. It seems obvious that this renders investigations of herb-drug interactions more complex than drug-drug interactions.

To make matters worse, herbal medicines are usually poorly standardized. One extract of St John's wort might therefore have a different profile of constituents than the next. This renders comparisons of results between different preparations problematic. Strictly speaking, we cannot extrapolate the findings obtained with one product to another.

4. Conclusions

This update shows that current research into herb-drug interactions is intense. Thus, we know that many such interactions are possible, of which some are sufficiently serious to endanger the health of our patients. It is therefore important that healthcare professionals are well informed about this fast-expanding field.

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