Pharmacokinetic interactions between drugs and dietary supplements: herbal supplements

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4.1 Introduction

Pharmacokinetics (PK) denotes the action of biological systems on drug absorption, distribution, metabolism and excretion (i.e. ADME – Figure 4.1), which directly relates to the amount of drug present in the blood stream or other body fluids (Henderson *et al*., 2002). Interference from a concomitantly ingested xenobiotic (i.e. drug, food, dietary supplement (DS)) with a drug's ADME may bear clinical significance, when drug plasma concentrations reach either toxic or sub-therapeutic levels (Kuhn, 2002). The extent of PK interactions depends on intervening factors that may be either drug- (dose, dose regimen, route of administration, therapeutic range, time of intake), patient- (race, age, weight, gender, state of health, pathology, genetic polymorphism, lifestyle), or xenobiotic-dependent (the amount and duration of exposure) (Skalli *et al*., 2007; Tomlinson *et al*., 2008; Gurley *et al*., 2008a). Patients subjected to complex treatment algorithms and polypharmacotherapy, elderly, pregnant and lactating women, cancer and HIV patients, people awaiting surgery, chronic patients, patients prescribed drugs with narrow therapeutic indices, and therapy non-responders are the most vulnerable population to abrupt alterations in drug PKs (Mallet *et al*., 2007; Skalli *et al*., 2007; Hermann and von Richter, 2012; (CDER), 2012; Bressler, 2005).

PK interactions are evaluated with *in vitro*/*in vivo* animal studies or in human trials. While *in vitro* research screens which DS may affect drug PKs, identifies PK targets susceptible to modulation by xenobiotics, and creates a platform for subsequent clinical studies, only the latter may provide a definitive means for determining whether statistically significant changes in drug plasma levels translate into clinically relevant outcomes (Butterweck *et al*., 2004; Gurley *et al*., 2008a). It is not uncommon for human trials to refute the *in vitro* or animal predictions, because the experimental designs in the these two models suffer from many drawbacks (Pal and Mitra, 2006; Venkataramanan *et al*., 2006; Skalli *et al*., 2007; Markowitz *et al*., 2008; Gurley *et al*., 2008b; Hermann and von Richter, 2012). Probe cocktails, a collection of relatively safe drug probes inactivated or eliminated primarily by a single metabolic process or transporter, and positive controls may be employed in

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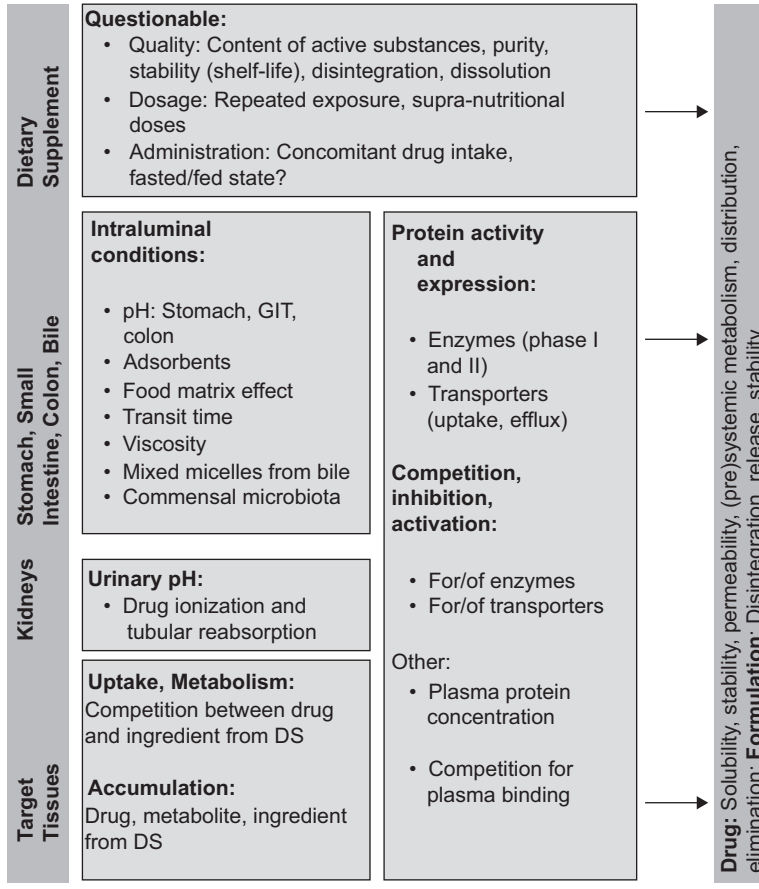

Figure 4.1 General principles of pharmacokinetics (PK) and possible targets for PK drug–dietary supplement interactions.

clinical trials to screen for possible changes in drug (pre-systemic) metabolism and excretion as a response to short-term or continued exposure to the DS (Tirona and Bailey, 2006). However, when considering DS–drug PK interactions, a number of other potential PK targets should also be explored, such as DS affecting *in vivo* drug/formulation performance by changing intraluminal conditions, which results in altered kinetics of drug release, drug stability, solubility, and/or permeability. Modification of drug distribution and tissue accumulation by DS may also be encountered.

Depending on the formulation, manufacturing process and physicochemical properties of allegedly active ingredients, the number of DSs available for consideration is prohibitive (MacDonald *et al*., 2009). Although <1% of all drug–DS interactions is actually reported (Chavez *et al*., 2006), dramatic case reports of possible interactions or exaggerated promotion of *in vitro* research may trump a well-controlled human

trial with actual PK data showing no interaction and unnecessarily alarm the consumers, causing a lack of compliance with prescribed therapy, or diversion from methods and means of scientific medicine. Health-care providers should therefore stay alert and offer clear-cut and useful guidance bearing clinical relevance in the case of drug–DS PK interactions.

4.2 Herbals: introduction

Herbal supplements are highly concentrated, complex mixtures of potentially active compounds with inherent pharmacological and/or toxicological properties (Venkataramanan *et al*., 2006). To avoid fluctuations in the content of the presumably active principles caused by growing, harvesting, and processing/manufacturing conditions, herbal supplements may be standardized; i.e. the quantity of marker compounds that occur naturally in the plant is standardized to ensure batch-to-batch consistency (Cupp, 1999). However, measurement and manipulation of marker compounds will not grant quality of the finished products, because many issues including adulteration, misidentification and contamination of the raw material continue to be a concern, while the production of a consistent product also entails routine evaluation of the finished product (impurities, solvent residues, dissolution/disintegration properties, labelling, storage and distribution conditions, stability testing, etc.) (Dog *et al*., 2010; Block, 2012).

With the widespread use of herbal supplements, PK herb–drug interactions seem inevitable, and a considerable body of work has been published in this regard. Unfortunately, the scientific literature has also become a reservoir of poorly-designed *in vitro* studies applying exaggerated, non-physiological concentrations of DS in their tests that bear little or no resemblance to actual plasma levels of the corresponding species. The reliability of *in vitro* results can also be undermined by the presence of compounds that play no part in PK interactions *in vivo* owing to their limited systemic bioavailability (for instance, unabsorbable tannins precipitate proteins *in vitro*, fluorescent substances may interfere with the analytics).

Many papers also disregard the fact that species potentially responsible for PK interactions may not be phytochemicals accountable for pharmacological activity (i.e. standardized markers). A well-executed *in vitro* study should thus acknowledge PK limitations of plant polyphenols, believed to be the carriers of health-beneficial effects and culprits of PK interactions (Figure 4.2), and strive to comply with the proposed guidelines for *in vitro* settings. Because the main players involved in PK interaction are not only phytochemicals but also their metabolites, further scientific scrutiny should be endorsed (Butterweck *et al*., 2004; Zhang *et al*., 2009).

It has been estimated that >150 herbs may be involved in drug interactions, while only 34 drugs were identified as the most likely candidates whose PKs could be affected by herbal DSs. The majority of the identified drugs includes CYP3A4, CYP2C9 (82.4%), Pgp (29.4%) or dual CYP3A4 and Pgp substrates (23.5%), drugs

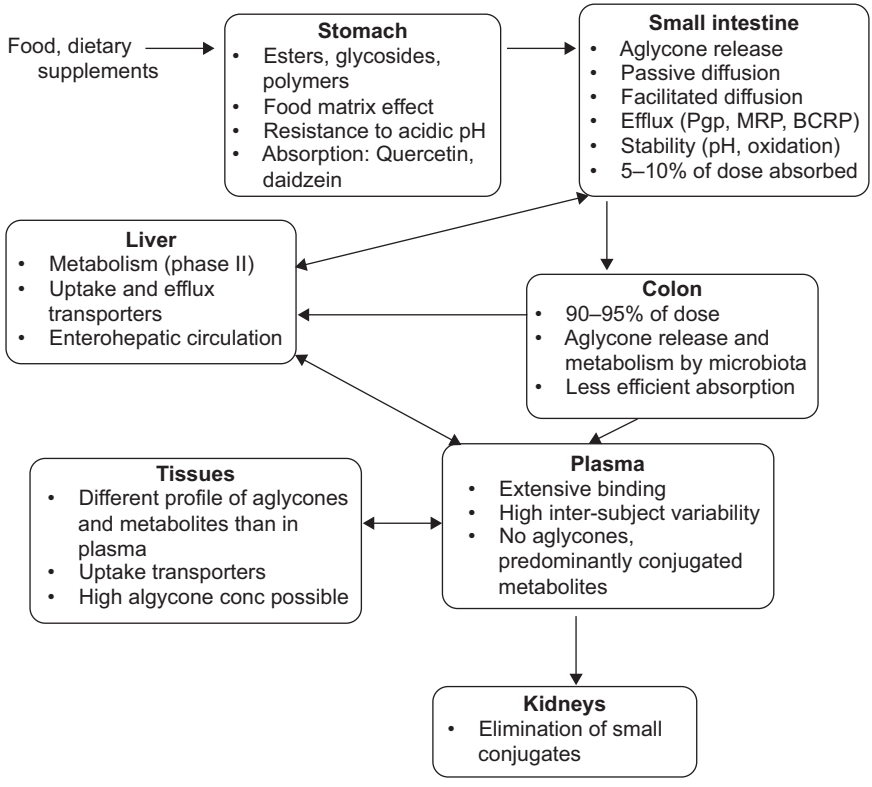

Figure 4.2 Pharmacokinetic destiny of polyphenols in humans.

intended for long-term use or substances with narrow therapeutic indices (Zhou *et al*., 2007; Sood *et al*., 2008).

Limited by the lack of data pertaining to the quality, identity and PK destiny of herbal products (i.e. phytoequivalence) and a wide variety of available brands, not even clinical trials may definitely answer whether a hidden risk of drug interactions exist in the case of herbal DSs (Pal and Mitra, 2006; Venkataramanan *et al*., 2006, Skalli *et al*., 2007; MacDonald *et al*., 2009).

Herbs containing mucilage polysaccharides (i.e. aloe, rhubarb, butternut, Iceland moss, European buckthorn, cascara, flax seeds, fenugreek, plantain, psyllium seed, etc.) are theoretically apt to bind simultaneously consumed drugs. Some may act as stool-softening and laxative agents, decreasing drug residence time at the absorption site. Salicylate rich botanicals (meadowsweet, black willow) may temporarily displace highly protein-bound drugs such as warfarin and sulfasalazine from plasma proteins, potentiating their pharmacological activities (Kuhn, 2002; Abebe, 2003; Bressler, 2005; Nutescu *et al*., 2006; van den Bout-van den Beukel *et al*., 2006; Zadoyan and Fuhr, 2012).

Clinical trials addressing PK drug–herb interactions for top-selling botanic products over the last decade are summarized in Table 4.1. Where none have been performed, *in vitro* data have been reviewed.

4.3 *Hypericum perforatum* (St John's Wort (SJW))

Besides quercetin, biapigenin, and hypericin, hyperforin is the main substance believed to affect drug PKs (Zhou *et al*., 2003; Pal and Mitra, 2006). Depending on the dosage and duration of use, no changes (i.e. midazolam) or increased exposure to prescribed drugs due to the inhibition of intestinal Pgp/CYP3A4 (i.e. voriconazole, fexofenadine) were observed in trials lasting up to 3 days (Izzo, 2005; Izzo and Ernst, 2009). Long-term SJW administration of more than 10 days causes a significant induction of hepatic CYPs (2C19, 2C8, 2E1), and CYP3A4 and Pgp in the liver and gut. No effect on CYP2D6, UGT1A1, and UGT1A9 expression or activity have been reported, while data on CYP1A2, CYP2C9 are controversial (Sparreboom *et al*., 2004; Tirona and Bailey, 2006; Venkataramanan *et al*., 2006; Nowack, 2008; Gurley *et al*., 2008a; Borrelli and Izzo, 2009; Rowe and Baker, 2009). More pronounced effects are expected with products richer in hyperforin (>10 mg/day) (Gurley *et al*., 2008a). After induction, CYP3A activity returns to basal levels progressively in approximately 1 week after cessation of SJW (Izzo and Ernst, 2009). Human trials evaluating 4–10-day exposure are lacking (Borrelli and Izzo, 2009).

Concomitant intake with drugs exerting extensive (pre)-systemic metabolism and/or narrow therapeutic indices is ill-advised. HIV patients on protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) should avoid SJW products (van den Bout-van den Beukel *et al*., 2006). For some drugs, monitoring and dose adjustments are necessary. Therapeutic manifestations triggered by SJW–drug PK interactions and possible therapeutic failure remains undetermined for alprazolam, chlorzoxazone, erythromycin, gliclazide, midazolam, nevirapine, simvastatin, tacrolimus, and verapamil. Paclitaxel, sirolimus, etoposide, doxorubicin and cyclophosphamide are also suspected to interact with SJW.

4.4 *Allium sativum* (garlic)

Clinical trials have failed to corroborate *in vitro*/*in vivo* animal PK predictions reporting significant modulation of PK targets by garlic products or organosulphur compounds (Zou *et al*., 2002; Izzo, 2005; Hu *et al*., 2005). Although a modest CYP2E1 inhibition was observed (Hermann and von Richter, 2012; Zadoyan and Fuhr, 2012), no notable or clinically relevant metabolism-based interactions are expected for CYP2E1 substrates, because except for chlorzoxazone, systemic clearance for other drugs does not rely solely on this isoform. Human trials seem to nullify any significant influence of garlic on drug PKs, but several PK targets (i.e. CYP2B1, 2B2, UGTs, GSTs, and transporters) have been identified to respond to garlic interventions *in vitro* and have not yet been explored *in vivo* (Hermann and von Richter, 2012).

Therefore, while the induction potential of garlic products seems clinically irrelevant, health-care providers should advise vigilance to patients on antiretrovirals and CYP2E1 substrates, because *in vitro* studies have highlighted important changes in the composition of different garlic DSs, which may explain perplexity pertaining to the potential for PK interactions (Borrelli *et al*., 2007).

Table 4.1 Human trials addressing pharmacokinetic herb–drug interactions for best-selling herbal DSs

Drug/probe	SJW	AS	GB	PG	PM	SR	EP
Alprazolam	IND$^{3A4,\ Pgp}$	N	N		? INH^{3A4}	N	
Aminopyrine							
Amitryptiline	IND$^{3A4\ (G+L),\ 2C19,\ Pgp}$						
Amoxicillin							
Anticonvulsants	#IND$^{3A4(G+L)}$						
Antipyrine			N				
Antiretrovirals	#IND^{3A4}, INH^{3A4,\ Pgp}$	? IND^{3A4}					
Atorvastatin	*#IND$^{3A4,\ Pgp}$						
Bupropion			N				
Buspiron							
Caffeine	N	N	N	N	N	N	INH^{1A2}
Carbamazepine	N						
Cefaclor							
Chlorzoxazone	IND^{2E1}	IND^{2E1}	N	N	N, INH^{2E1}	N	N
Clopidogrel	IND^{3A4}						
Cortisol	IND^{3A4}		N	N			
Coumarin							
Cyclophosphamide	?						
Cyclosporin A	*#IND$^{3A4,\ Pgp}$, INH^{Pgp}	N					
Dapsone			IND$^{N\text{-}Ac\text{-}T}$				
Darunavir							IND$^{3A4(L)}$
Debrisoquine	N	N	N	N	N	N	N
Desogestrel	INH$^{2C9/2C19}$ and/or IND^{3A4}						
Dextromethorphan	N	N	N			N	N
Diazepam			$^{\alpha}$N				
Diclofenac			N				
Diltiazem			INH^{3A4}				
Digoxin	IND^{Pgp(G+L)}		$^{\alpha}$N	INH$^{3A4(G)}$	N		N
Docetaxel		N	N				
Donepezil							
Doxorubicin							
Erythromycin	IND^{3A4}						
Ethinylestradiol	IND^{3A4}						
Etoposide							
Fexofenadine	*IND^{Pgp}		N				
Flurbiprofen			N				

WM	SM	HC	VO	CR	GM	CS	VV	CL
			N, INH[3A4]			N		
	N							
N								
						N	INH[3A4]	
	N	N	N	N	INH[1A2], IND[2A6]	N	IND[1A2]	INH[1A2], IND[2A6]
N								
	N	N	N	N				
					N			
	N							
N	N	INH[3A4]					?	
	N	N, INH[2D6]	N	N				
		INH[2D6]	N			N	INH[2D6]	
N								
	N	INH[Pgp(G)]		N				
	N							
N								

Continued

Table 4.1 Continued

Drug/probe	SJW	AS	GB	PG	PM	SR	EP
Gliclazide	α?^{2C9}						
Imatinib	*#IND$^{3A4, Pgp}$						
Indinavir	#IND$^{3A4, Pgp}$						
Irinotecan	#IND$^{3A4, Pgp(?)}$						
Iron							
Ivabradine	IND$^{3A4(G+L)}$						
Ketodesogestrel	IND^{3A4}						
Levothyroxine							
Lidocaine	IND^{3A4}						
Lopinavir	?		N				N
Losartan							
Mephenytoin	IND$^{2C19(wild type)}$		N				
Methadone	IND$^{3A4, Pgp}$						
Metronidazole							
Midazolam	IND$^{3A4(G+(L?)), Pgp}$	N	αN, INH^{3A4}	N	N	N	INH$^{3AG(G)}$, IND$^{3A4(L)}$
Mycophenolic acid	N						
Nelfinavir	IND^{3A4}						
Nevirapine	IND$^{3A4, 2B6(?), Pgp}$						
Nifedipine	IND^{3A4}		αN	INH$^{3A4(G)}$			
Norethindrone	IND^{3A4}						
Nortriptyline	IND$^{2D6(?)}$						
Omeprazole	IND$^{3A4, 2C19}$		α IND(?)$^{2C19, 3A4}$				
Oral contraceptives	#IND$^{3A4(G+L)}$						
Oxycodon	INH^{3A4}						
Paracetamol		N					
Paclitaxel							
Phenprocoumon	IND$^{3A4>2C9}$						
Phenylbutazone							
Phenytoin			N				
Pravastatin	N						
Prednisone	N						
Quazepam	IND$^{3A4, 2C19, Pgp}$						
Ranitidine							
Ritonavir	IND$^{3A4, Pgp}$	?	?				N
Rosiglitazone	IND^{2C8}						
Rosuvastatin							
Saquinavir	?	?					
Simvastatin	IND$^{3A4, Pgp}$						
Sirolimus							
Statins	α#IND$^{3A4(G+L), Pgp}$, INH^{Pgp}						
Tacrolimus	*IND$^{3A4, Pgp}$						
Talinolol	IND^{Pgp}						

WM	SM	HC	VO	CR	GM	CS	VV	CL
	N	N						
	N				INH^{Abs}			
					INH^{Abs}			
	N	INH^{2C9}			N	N	IND^{2C9}	
	N							
	$IND^{3A4,Pgp(G)}$							
N	N	N, INH^{3A4}	N	N			N	
	N							
		N						
	N							
	N							
	N							
	N							

Continued

Table 4.1 Continued

Drug/probe	SJW	AS	GB	PG	PM	SR	EP
Theophylline	#N, IND$^{3A4(G+L),\ 2E1}$						
Tibolone	?						
Ticlopidin			N				
Tizanidine							
Tolbutamide	N		N, INH^{2C9}				N
Trazodone			?IND^{3A4}				
Verapamil	*#IND$^{3A4(G+L),\ Pgp}$						
Vinblastine	?						
Voriconazole	IND$^{2C19,\ 3A4,\ Pgp}$		N				
Warfarin	#IND$^{3A4(G+L),\ 2C19,\ 1A2(?)}$	N	N	#αIND$^{2C9(?)}$			N

IND – induction; INH – inhibition; N – no effect; G – gut; L – liver; 1A2 – CYP1A2; 2C9 – CYP2C9; 2C19 – CYP2C19; 2E1 – CYP2E1; 3A4 – CYP3A4; 2D6 – CYP2D6; Pgp – P-glycoprotein; OATP – Organic Anion Transporting Protein; Abs – absorption;? – unknown/speculated; N-Ac-T – N-acethyl transferase; > – the predominant/main interaction mechanism; * – adjust dose; # – avoid combination; $ – combination is contraindicated; α – close monitoring advised.
SJW – *Hypericum perforatum;* AS – *Allium sativum;* GB – *Ginkgo biloba;* PG – *Panax ginseng;* PN – *Piper methysticum;* SR – *Serenoa repens;* EP – *Echinacea purpurea;* VM – *Vaccinium macrocarpon;* HC – *Hydrastis canadensis;* VO – *Valeriana officinalis;* CR – *Cimicifuga racemosa;* GM – *Glycine max;* CS – *Camelia sinensis;* VV – *Vitis vinifera;* CL – *Curcuma longa*.

4.5 *Ginkgo biloba* (ginkgo)

In vitro studies identified ginkgolic acid I and II as potent CYP inhibitors. Other ginkgo constituents with even higher systemic bioavailability than ginkgolic acid (F_{abs} > 70%), showed moderate effects on CYPs bearing no *in vivo* relevance (Zou *et al*., 2002; Zhang *et al*., 2010). Although ginkgo–drug interactions seem unlikely at recommended doses (no effect on CYPs, OATPs, OCTs, OCTNs, MATEs), co-administration with CYP2C19 substrates should be avoided by poor CYP2C19 metabolizers (Izzo and Ernst, 2009; Zuo *et al*., 2010).

Owing to significant changes in gene expression observed in mice for phase I (CYP), II (glutathione-S-transferase, sulfotransferase), and III (solute carrier proteins, ATP-binding cassette proteins) proteins after 2-year exposure to ginkgo (Markowitz *et al*., 2003; Guo *et al*., 2010; Kim *et al*., 2010) accompanied by a lack of agreement regarding ginkgo impact on CYP3A4, 2C9 and 2C19 (Yoshioka *et al*., 2004), this herb may interfere with PKs of anticancer drugs, anticonvulsants, and UGT and CYP2C19 substrates (Sparreboom *et al*., 2004; Izzo and Ernst, 2009; Hermann and von Richter, 2012). Exercising self-administration of ginkgo products should thus be discouraged in elderly or in patients using prescribed drugs with narrow therapeutic indices (Uchida *et al*., 2006).

WM	SM	HC	VO	CR	GM	CS	VV	CL
N					INH^{1A2}	INH^{1A2}		
$^{\#}INH^{2C9(?)}$					$?INH^{Pgp,\ OATP\ (?)}$			

4.6 *Panax ginseng* (ginseng), *Piper methysticum* (kava kava) and *Serenoa repens* (saw palmetto)

Although no significant impact on CYP expression/activity was observed, a brand-specific impact on CYP3A4 substrates may be anticipated as demonstrated for digoxin and nifedipine (Sparreboom *et al*., 2004; Zadoyan and Fuhr, 2012). Slight inhibition of CYP2D6 was observed in elderly (Izzo and Ernst, 2009), while studies with warfarin are inconclusive. Siberian ginseng (*Eleutherococcus senticosus*) has no impact on CYP3A4, and 2D6, while American ginseng (*Panax quinquefolius*) does not influence UGT2B7. Siberian ginseng should be avoided during antiretroviral therapy, while its effect on warfarin is inconclusive (Zadoyan and Fuhr, 2012).

In the case of *Piper methysticum* (kava kava), clinical recommendations regarding the PK interaction of kava administration with drugs are mainly based on theoretical considerations. Patients taking anticancer, hepatotoxic drugs, and CYP2E1 and 3A4 substrates should be routinely monitored (Anke and Ramzan, 2004; Sparreboom *et al*., 2004; Gurley *et al*., 2005; Zadoyan and Fuhr, 2012). Case reports regarding kava-associated hepatotoxicity resulted in product withdrawal from the US and EU market in 2002 (Sarris *et al*., 2009; Rowe *et al*., 2011). Later publications revealed that patients with CYP2D6 polymorphism (poor metabolizers) are at higher risk of adverse reactions due to insufficient kavalactone metabolism (i.e. detoxification), while for most kava consumers, kava products do not raise safety issues (Rowe *et al*., 2011).

Saw palmetto extract at generally recommended doses poses minimal risk for drug disposition dependent on CYP3A4 and 2D6 pathways. Unfortunately, other potential targets for PK interactions (enzymes/transporters) have not been evaluated; therefore these findings cannot be extended to other supplements or drugs (Gordon and

Shaughnessy, 2003; Gurley *et al*., 2004; Chavez *et al*., 2006; van den Bout-van den Beukel *et al*., 2006; Nowack, 2008; Izzo and Ernst, 2009; Zadoyan and Fuhr, 2012).

4.7 *Echinacea purpurea* (purple coneflower), *Vaccinium macrocarpon* (cranberry) and *Silybum marianum* (milk thistle)

The probability of *Echinacea* triggering worrisome metabolism-/transporter-based interactions involving CYP1A2, 2C9, 2D6, 2E1 and Pgp in the general population is small (Gurley *et al*., 2004; Izzo and Ernst, 2009; Hermann and von Richter, 2012). However, seemingly minor changes in the activity of CYP1A2 and 3A4 merit further studies; therefore concomitant use with the corresponding substrates should be discouraged. *Echinacea* selectively inhibits intestinal and induces hepatic CYP3A4, thus creating two counteracting mechanisms in terms of net effect on systemic drug bioavailability (Gurley *et al*., 2008a; Nowack, 2008), which ultimately may lead to clinically relevant decrease in exposure to poorly bioavailable CYP3A4 substrates. In the case of antiretrovirals, low capacity of altering ritonavir-boosted PI PKs has been demonstrated (Hermann and von Richter, 2012). Case-by-case recommendations are needed for cancer and asthma patients.

In the case of cranberry (*Vaccinium macrocarpon*), based on little available data, no significant interactions may be expected with CYP3A4, 1A2, 2C9 and PepT1, PepT2 substrates with daily consumption not exceeding one glass of cranberry juice (Sparreboom *et al*., 2004; Li *et al*., 2009; Zadoyan and Fuhr, 2012). In general, rapid absorption and urinary elimination result in tissue bioavailability and low plasma levels of anthocyanins (bioavailability is <1% of dose; plasma levels 0.56–4.64 nM). However, plasma anthocyanin levels may not correctly reflect anthocyanin activity, because tissue accumulation and thus gene expression changes are possible during prolonged consumption (Milbury *et al*., 2010). Caution should be advised for patients on antiretrovirals, warfarin and other CYP3A4 and 2C9 substrates, because anthocyanins are potent *in vitro* inhibitors of both isoenzymes (Nutescu *et al*., 2006; van den Bout-van den Beukel *et al*., 2006; Greenblatt *et al*., 2006; Uesawa and Mohri, 2006; Gohil and Patel, 2007; Nowack, 2008). Salicylates in cranberry juice may displace warfarin from plasma proteins (Duthie *et al*., 2005).

In the case of milk thistle (*Silybum marianum*), no clinically relevant interactions through CYPs, UGT1A1, breast cancer resistance protein (BCRP) or OATP1B1 are expected even at supra-therapeutical doses because plasma levels of free and conjugated silymarin species (reported range 0.024–1.3 μg/mL) are significantly below IC_{50} (25–250 μM) values owing to insufficient solubility and dissolution kinetics of milk thistle DS, and high inter-subject variability (Gurley *et al*., 2004; Venkataramanan *et al*., 2006; Mohamed and Frye, 2011; Hermann and von Richter, 2012; Zadoyan and Fuhr, 2012). Although there are indications of decreased systemic exposure to CYP3A4 and Pgp substrates (i.e. indinavir), clinical trials do not support the premises of altered CYP3A4/Pgp expression/activity (Hermann and von Richter, 2012). As

a precaution, concomitant medication with CYP3A4/Pgp substrates exerting low systemic bioavailability and milk thistle DS should be avoided (Gurley *et al*., 2006b; Zadoyan and Fuhr, 2012). An increased intra-luminal concentration of milk thistle flavolignans (40–1200 μg/mL predicted) reaching IC_{50} values may be expected during the use milk thistle DS formulated with dissolution enhancer phosphatidylcholine, which, combined with extensive enterohepatic circulation of these phytochemicals, raises the probability of intraluminal PK interactions (Gurley *et al*., 2004; De Smet, 2007; Mohamed and Frye, 2011).

4.8 *Hydrastis canadensis* (goldenseal), *Valeriana officinalis* (valerian) and *Cimicifuga racemosa* (black cohosh)

Goldenseal extract is a mild to moderate CYP3A4, 3A5, 2D6 and Pgp inhibitor; therefore patients should refrain from its concomitant use with prescription medications with narrow therapeutic indices, or drugs which rely extensively on these isoenzymes for systemic clearance (Fuchikami *et al*., 2006; Zadoyan and Fuhr, 2012; Hermann and von Richter, 2012). Mixed results may be found regarding clinical relevance of goldenseal-CYP3A4 substrates interactions; no effect on indinavir PKs has been reported, while cyclosporine A plasma levels increased (Gurley *et al*., 2005; Nowack, 2008). No trials were found regarding goldenseal impact on CYP2C9 and 2C19.

Pharmacologically active valepotriates, valerenic acid and alkaloids do not affect CYP activities or expression in humans even after multiple dosing (Sparreboom *et al*., 2004; Nowack, 2008), most probably due to lower quantities of these active principles resulting from high variability in DS composition and high instability of marker phytochemicals (Heiligenstein and Guenther, 1998). Additionally, valerenic acid attains significantly lower plasma levels (0.9–2.3 ng/mL) than necessary for modulation of CYPs (IC_{50} 5–10 μM) (Anderson *et al*., 2005). Interactions in intestinal lining were suggested, because a 500–1000 mg of valerian extract could yield sufficiently high intraluminal concentration to inhibit UGTs (Mohamed and Frye, 2011).

Pharmacologically active phyto-constituents in black cohosh have not yet been identified (Sparreboom *et al*., 2004). While *in vivo* evidence seems to render black cohosh an unlikely source of clinically relevant interactions through CYP1A2, 2D6, 3A4, 2E1 or Pgp, concomitant administration with atorvastatin is not recommended due to suspected CYP3A4 inhibition (Gurley *et al*., 2006a; Dog *et al*., 2010; Zadoyan and Fuhr, 2012).

4.9 *Glycine max* (soy), *Camellia sinensis* (green tea) and *Zingiber officinale* (ginger)

Isoflavonoids (daidzein, genistein, glycitein) inhibit CYP1A2, 2E1, GLUT1,4 and induce CYP1A2, 1A1, and 2A6. Their pro-catabolic effect on sex hormones was

mediated through CYP1A1 and 1A2 induction (Nakajima *et al*., 2006, Wood *et al*., 2007). Soy isoflavonoids exert rapid absorption, BCRP-limited distribution to brain, testes, and foetus, and rapid elimination (Roberts *et al*., 2004; Enokizono *et al*., 2007; Burnett *et al*., 2011). More than 95% of plasma isoflavonoids is glucuronated and exhibits extensive enterohepatic circulation (Burnett *et al*., 2011). Daidzein, genistein and glycetin plasma levels (5 μM) are in the range of determined K_i or IC_{50} values, thus CYP2A6*1 (0.7–6 μM) or UGT2B17 (4.6 μg/mL) inhibition is possible (Nakajima *et al*., 2006; Mohamed and Frye, 2011). The safety of soy consumption has been questioned during concomitant medication with CYP1A2, and 3A4 substrates (PIs, NNRTIs) and in infants with congenital hypothyroidism, where decreased levothyroxine absorption was noticed (Conrad *et al*., 2004; Zadoyan and Fuhr, 2012).

In the case of green tea (camellia sinensis), repeated catechin ingestion is unlikely to result in modified drug disposition by CYPs (van den Bout-van den Beukel *et al*., 2006, Nowack, 2008; Zadoyan and Fuhr, 2012), while a decreased drug and calcium absorption may occur (Kuhn, 2002; Abebe, 2003). Data from *in vitro* and *in vivo* rodent studies indicate inhibition of intestinal UGT1A1, which could affect raloxifene and ezetimibe PKs (Mohamed and Frye, 2011). Gallated polyphenols were also shown to inhibit OATP1B1, 1B3 and 2B1 with IC_{50} values (7–10 μM) attainable *in vivo* with 1600 mg dose of epigallocatechingallate. Interactions outside the gut are unlikely due to extensive intestinal phase I, II, and III metabolism of green tea phytochemicals (metabolism is saturable at doses higher than 1600 mg) (Cai *et al*., 2002; Roth *et al*., 2011). Inhibition of MCT, SGLT1 and Pgp by tea polyphenols has also been communicated in the literature (Konishi *et al*., 2003) but no clinically relevant interactions have been reported.

Caution is advised when ginger is taken concomitantly with anticoagulants, whose metabolism depends on CYP3A4 and 2C9 (Zuo *et al*., 2010). No interactions with drugs are known (Akram *et al*., 2011), probably because only pharmacologically inert conjugates of ginger constituents have been detected in plasma (0.01–1.2 μg/mL range) (Yu *et al*., 2011). 6-gingerol is the only phytochemical exerting measurable absorption that could trigger PK interactions (Zick *et al*., 2008). *In vivo* animal research reported significantly decreased cyclosporine A and increased metronidazole bioavailability due to CYP-mediated interaction (Okonta *et al*., 2008).

4.10 *Morinda citrifolia* (noni), *Aloe vera* (aloe), *Vitis vinifera* (grape seed) and *Curcuma longa* (turmeric)

Rapid absorption, rapid elimination and uricosuric effect of scopoletin (purportedly active phytochemical in noni) were noticed in animal studies (Wang *et al*., 2002). Noni juice affected gastric transit time, interacted with Cyp3A in disease- and age-specific manner, increased GST activity after single dose and inhibited UGTs during chronic administration with no Pgp effect in rodent studies (Engdal and Nilsen, 2008; Mohamed and Frye, 2011). No interactions with drugs have been published. A complete list of ingredients may be found in (Pawlus and Kinghorn, 2007).

In the case of aloe vera, significantly increased vitamin C and E absorption were observed during concomitant ingestion, making aloe DS a potential adjunct for people taking vitamin supplements. Since glucuronidation of anthaquinones from aloe presents the main elimination pathway, interactions with extensively glucuronated drugs zidovudine and lamotrigine should be explored.

In the case of grape seed (*Vitis vinifera*), CYP2C9 and 2D6 inhibition, CYP1A2 induction and mixed reports about CYP3A4 effect may be found in the literature, suggesting caution for cancer patients on high-dose grape seed extracts (Sparreboom *et al*., 2004). Resveratrol and ε-viniferin are potent CYPs, Pgp, OATP-B, and xanthine oxidase inhibitors *in vitro* (Piver *et al*., 2003, Nabekura *et al*., 2005; Etheridge *et al*., 2007; Zadoyan and Fuhr, 2012). Plasma (ng/mL levels) and tissue accumulation of resveratrol and its conjugates may be expected after multiple daily administrations (Chow *et al*., 2010).

Instability, rapid absorption and extensive pre-systemic metabolism hinder curcumin systemic bioavailability (plasma levels are in nM range), which may at least partially be overcome by formulating curcumin with dissolution/permeation enhancers (i.e. piperine) (Oetari *et al*., 1996; Thapliyal *et al*., 2002; Sharma *et al*., 2005). *In vitro* curcumin potential to modify several CYPs, UGTs, GSTs has been established (Firozi *et al*., 1996; Nowack, 2008; Nayak and Sashidhar, 2010). Based on IC_{50} values, interactions in the intestine seem possible (CYP2C9; IC_{50} 4.3 μM). Saturation of human pre-systemic metabolism may be achieved at supra-doses of 8–12 g/day, which could lead to erratic blood levels of CYP substrates *in vivo* (Sharma *et al*., 2005).

4.11 *Stevia rebaudiana* (stevia), *Lepidium meyenii* (maca) and *Garcinia mangostana* (mangosteen)

Stevia is a high-potency bio-sweetener (Das *et al*., 2005). Competition between aglycone steviol released by commensal microbiota in colon and drugs for transporters in intestine is questionable. Steviol showed significant accumulation in rodent liver, kidney and intestine. In humans, steviol and its glucuronides plasma levels are low; 121 ng/mL and 1.89 μg/mL, respectively. Urinary elimination is the predominant excretion pathway, and it includes active tubular secretion with OATs, OCTs or OATP4C1 as possible candidates. Since the accepted daily intake of 5 mg/kg does not assure plasma levels close to IC_{50}, steviol should not influence renal drug elimination (Srimaroeng *et al*., 2005; Chatsudthipong and Muanprasat, 2009).

Ingestion of cooked maca (lepidium meyenii) significantly increased total plasma proteins and albumins, changing progesterone and testosterone plasma levels in mice, which was not corroborated in postmenopausal women (Brooks *et al*., 2008; Coates, 2010). No drug interactions have been reported.

Although pure mangosteen juice contains c.5 mM xanthones, maximal plasma levels after 60 mL of juice ingestion were highly variable and only 0.1 μM for α-mangostin (levels of other species were even lower). Fed conditions aided absorption through lymph (F_{abs} = 2% of dose). Prolonged exposure to α-mangostin significantly

increased its tumour concentrations in mice, while *in vitro* studies indicated CYP2C9 inhibition (Hidaka *et al*., 2008; Chitchumroonchokchai *et al*., 2013). No interactions with drugs have been reported.

4.12 Summary

Key points to note are:

- Numerous brands of herbal supplements available in different dosage forms exist. Human trials have indicated that a clinically significant interaction may occur during concomitant use with drugs depending on drug-, patient-, and herb-associated factors. Compared to the number of potential PK targets and available quantity of herbal DS (c.150) the number of identified and clinically relevant interactions is low (<10).
- Because the complete composition is usually unknown, no clinical study can prove phytoequivalence. Thus, results from one study may not be generalized for all DSs of the same herb.

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