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REVIEW ARTICLE

Interaction between phytotherapy and oral anticancer agents: prospective study and literature review

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Abstract

Cancer is becoming more prevalent in elderly patient. Due to polypharmacy, older adults with cancer are predisposed to drug-drug interactions. There is also an increasing interest in the use of complementary and alternative medicine (CAM). Thirty to seventy percent of patients with cancer have used CAM. Through pharmaceutical counseling sessions, we can provide advices on herb–drug interactions (HDI). All the patients seen in pharmaceutical counseling sessions were prospectively included. Information was collected during these sessions: prescribed medication (oral anticancer agents (OAA) and other drugs), CAM (phytotherapy especially), and use of over-the-counter (OTC) drugs. If pharmacist considered an interaction or an intervention clinically relevant, the oncologist was notified. Then, a literature review was realized to identify the potential HDI (no interactions, precautions for use, contraindication). Among 201 pharmacist counseling sessions, it resulted in 104 interventions related to 46 HDI, 28 drug-drug interactions and 30 others (wrong dosage, omission…). To determine HDI, we review 73 medicinal plants which are used by our patients with cancer and 31 OAA. A total of 1829 recommendations were formulated about 59 (75%) medical plants and their interaction with an OAA. Herb–drug interactions should not be ignored by healthcare providers in their management of cancer patients in daily practice.

Keywords Oncology · Oral anticancer agents · Phytotherapy · Herb–drug interactions

Introduction

Iatrogenic complications are frequent in elderly patients (aged 65 years or older) because of the increased number of comorbidities, resulting in a larger number of prescribed drugs (polypharmacy) [1]. Thus, older adults with chronic disease, especially with cancer, are predisposed to drug-drug interactions. Recent studies suggest that the risk of drug-drug interaction is common, in particular since the advent of oral anticancer agents (OAA) (i.e., oral antineoplastic agents such as hormonotherapy and chemotherapy—and targeted therapy) [2–6].

Drug-drug interactions are either pharmacokinetic or pharmacodynamic [7–9]. Most pharmacokinetic interactions may result from inhibition or induction of cytochrome P450 (CYP) enzymes, or from transport proteins [for instance: Uridine diphosphate-glucuronosyltransferase (UGT), P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP)] [10–12]. They can increase or decrease the exposure of the OAA and cause adverse events or treatment failure. Most OAA, and especially targeted therapies, are metabolized by the liver and are greater risks of drug-drug interactions [13]. Thus, interactions between targeted therapies and other prescribed and over-the-counter medicines, complementary medicines and food can affect the efficacy and safety of both, the targeted therapy and the other therapy. It is important to fully assess the potential interactions when a patient starts a therapeutic regimen, or when any new drugs are given.

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Nevertheless, to our knowledge there is no referential which permits a quick analysis of HDI with OAA.

Complementary and alternative medicines (CAM) is defined by the World Health Organization as healthcare practices that are not part of a given country's own traditions, nor have they become integrated into its mainstream healthcare system [14]. More and more patients with a diagnosis of cancer, between 30 and 70%, are using CAM during chemotherapy [15–20]. CAM are used for treating cancer or other diseases or symptoms, without taking into account the risk of HDI. However, interactions between CAM and conventional drugs are numerous [7, 20–23]. For instance, in a recent study, nearly 400 healthcare professionals in the Middle East identified the use of 44 herbs, and 15 have HDI with intravenous antineoplastic agents [24].

Along with the growing use of OAA, and especially targeted therapies, the potential problem of interactions with other medicinal products as well as other forms of interaction needs to be taken into account in patient management. Providing clear and appropriate drug instructions is an important new challenge for OAA.

Pharmacists are key members of a multidisciplinary team and readily accessible to patients, both in the community and in hospital settings. So, they play a significant role in managing these cancer patients due to their expertise and knowledge of medicines [25]. Community and clinical pharmacists are required to provide specific drug instructions and supportive care counseling about the prevention and treatment-related adverse events. Community and hospital pharmacists can therefore make a significant contribution to reducing the risk of interactions and optimize patients' treatment [26–28].

In this context, the aim of this study was to systematically identify and review published herb–drug interaction related articles based on potential HDI with OAA identified in daily practice. The first part of this work assessed the interest of pharmacist counseling sessions in a prospective cohort of patients receiving OAA; the second part is a systematic literature review on HDI.

Methods

Pharmaceutical interventions in daily practice

All consecutive patients treated in a University hospital with a first prescription of OAA and pharmacist counseling sessions between the January 1, 2016, and the June 30, 2017, were prospectively included in the analysis.

During pharmacist counseling sessions, the new treatment and potential drug-drug interactions or HDI were explained to the patients. This included other prescribed drugs for cancer or comorbidities. Pharmacist counseling sessions focus on OAA for solid tumors: breast cancer (capecitabine, cyclophosphamide, etoposide, everolimus, lapatinib, palbociclib, vinorelbine), kidney cancer (axitinib, cabozantinib, everolimus, pazopanib, sunitinib), colon, rectal and gastrointestinal cancer (imatinib, capecitabine, regorafenib), ovary cancer (cyclophosphamide, olaparib), prostate cancer (abiraterone, enzalutamide), lung cancer (afatinib, crizotinib, etoposide, vinorelbine, erlotinib, gefitinib, lomustine, osimertinib), thyroïd cancer (lenvatinib, vandetanib), skin cancer (cobimetinib, dabrafenib, lomustine, trametinib, vemurafenib, vismodegib), liver cancer (everolimus, regorafenib, sorafenib) and brain cancer (lomustine, temozolomide).

For each patient with pharmaceutical counseling sessions, relevant information was collected prospectively: sociodemographic data, cancer type, OAA starting date, ambulatory treatment, self-medication, use of CAM and its name. A leaflet concerning the new cancer treatment was explained and given to the patient during this pharmacist counseling session. It included general information on availability, retention of treatment, how it is taken, side effects and advices on its use. A thorough search for possible interactions was then carried out by the pharmacist: interactions between the anticancer agent and the drugs delivered in outpatient care or interactions between the anticancer agent and CAM, including herbal medicine. This search consisted of a systematic review in Pubmed. The interactions and pharmaceutical interventions were collected [29].

Following this analysis, the pharmacist contacted the oncologist to inform for a potential interaction, if it was clinically relevant. The oncologist could decide to consult the patient again to inform him of the potential risk. Thus, when a plant is not recommended, pharmacists preferred to indicate that it was forbidden. When a plant could bring about an interaction with an anticancer drug, the association should be avoided.

A review of the pharmacist counseling sessions is available on the patient's computerized oncology record (DCC®). This report was also sent to the ambulatory doctor and community pharmacist.

Literature review

After identification of potential HDI, relevant articles were selected from the Micromedex database and MEDLINE without any chronological restrictions (deadline November 2018) in French and English. The search terms (referenced as MeSH terms) were: the medicinal plants mentioned by our patients during interviews (English and Latin denominations were both used) OR "herb–drug interaction" OR "Phytotherapy" AND "Cytochrom" OR "Transporter" AND "Antineoplastic" OR "Abiraterone" OR "Afatinib" OR "Axitinib" OR "Cabozantinib" OR "Capecitabine" OR "Cobimetinib" OR "Crizotinib" OR "Cyclophosphamide" OR "Dabrafenib"

OR "Enzalutamide" OR "Erlotinib" OR "Etoposide" OR "Everolimus" OR "Gefinitib" OR "Imatinib" OR "Lapatinib" OR "Lenvatinib" OR "Lomustine" OR "Olaparib" OR "Osimertinib" OR "Palbociclib" OR "Pazopanib" OR "Regorafenib" OR "Sorafenib" OR "Sunitinib" OR "Temozolomide" OR "Trametinib" OR "Vandetanib" OR "Vemurafenib" OR "Vinorelbine" OR "Vismodegib". The articles were selected based on title and summary content.

Additional publications were identified by checking all reference lists of selected articles. Furthermore, previous reviews dealing with HDI were also investigated for further relevant information.

The chosen articles were screened and analyzed by one reviewer (ALC) and checked by a second reviewer (MBJ) to determine whether or not a given article was both relevant and interesting. A consensus was found in the case of disagreements between the two reviewers. The main reason for excluding an article was recorded.

For every OAA, its pharmacokinetics was explained (inducer, inhibitor or substrate of cytochrome, transporter…). Then, a double entry table summarized HDI. Three risk level of each association between plants and OAA were determined: level 1 (no interaction), level 2 [precaution for use: same interaction (Oral anticancer agent and plant inhibit or induce the same CYP or transporter)] and level 3 (interaction or toxicity described in literature).

Statistical analysis

Continuous variables were described by mean standard deviation and median (range), and qualitative variables by size and percentage. Chi square test was performed to compare the populations and was significant at a threshold of 5% (*P* value). Statistical analyses were performed by Excel®.

Results

Pharmaceutical interventions in daily practice

From the January 1, 2016, to the June 30, 2017, 201 pharmacist counseling sessions were carried out. One hundred and eighty-eight patients had at least one initial pharmacist counseling session (Table 1). Thirteen patients had two pharmacist counseling sessions. Twenty-seven percent of patients took at least one CAM, in addition to their anticancer treatment. For 19.0% of them, the CAMs used included at least one plant.

Pharmaceutical interventions concerned 31.3% of pharmaceutical counseling sessions ($n=63$) (Fig. 1). In total, 104 pharmaceutical interventions were performed. Twenty-eight were drug-drug interactions and 46 HDI. Thirty were related to over- or underdosage or omission of supportive drugs.

Table 1 Characteristics of patients with oral anticancer agents and pharmaceutical counseling sessions

	$n=201$	%
Patient number (*n*, %)	188	
Male	77	41.0
Female	111	59.0
Age (years)	66.4	(54.0–78.8)
Cancer (*n*, %)		
Breast cancer	59	31.4
Kidney cancer	35	18.6
Prostate cancer	17	9
Lung cancer	14	7.4
Brain cancer	14	7.4
Skin cancer	11	5.8
Bone cancer	10	5.3
Colon cancer	7	3.7
Others (pancreatic, ovarian, etc.)	21	11.2
No. of drugs used per patient	7	(1–18)
Including		
Anticancer agent	1	(0–3)
Supportive drugs	2	(0–8)
Drugs for comorbidities	3	(0–13)
CAM	2	(0–14)
Including herbs	2	(0–15)

CAM complementary and alternative medicines, *No* number

Thirty-one OAA and 73 plants were identified and studied. All the HDI concerned the OAA and were based on systematic review. The rate of herb–OAA interaction is 15%: 29 prescriptions for 188 patients receiving pharmaceutical counseling. Twenty-six herbs had an interaction with 11 OAA (Abiraterone, afatinib, capecitabine, enzalutamide, erlotinib, everolimus, gefitinib, palbociclib, pazopanib, sorafenib, sunitinib) (Table 2). Thirteen plants were found at least twice: corossol, turmeric, thyme, verbena, peppermint, red yeast rice, fermented wheat germ extract, grape seed, German chamomile, gingko, pineapple, hibiscus.

Literature review

The literature search identified 319 articles, among which 27 were duplicates and 131 were excluded after screening and analysis of titles and abstracts because they did not match the eligibility criteria. A total of 161 were eligible for systematic review. One hundred and forty-eight additional publications were identified by checking all articles' bibliographies. Ninety-eight publications were involved with OAA; 110 with pharmacokinetic of plants, 3 with herb–OAA interactions and 28 were literature review.

The metabolism and the transport of OAA were synthetized in Tables 3, 4 [30–149].

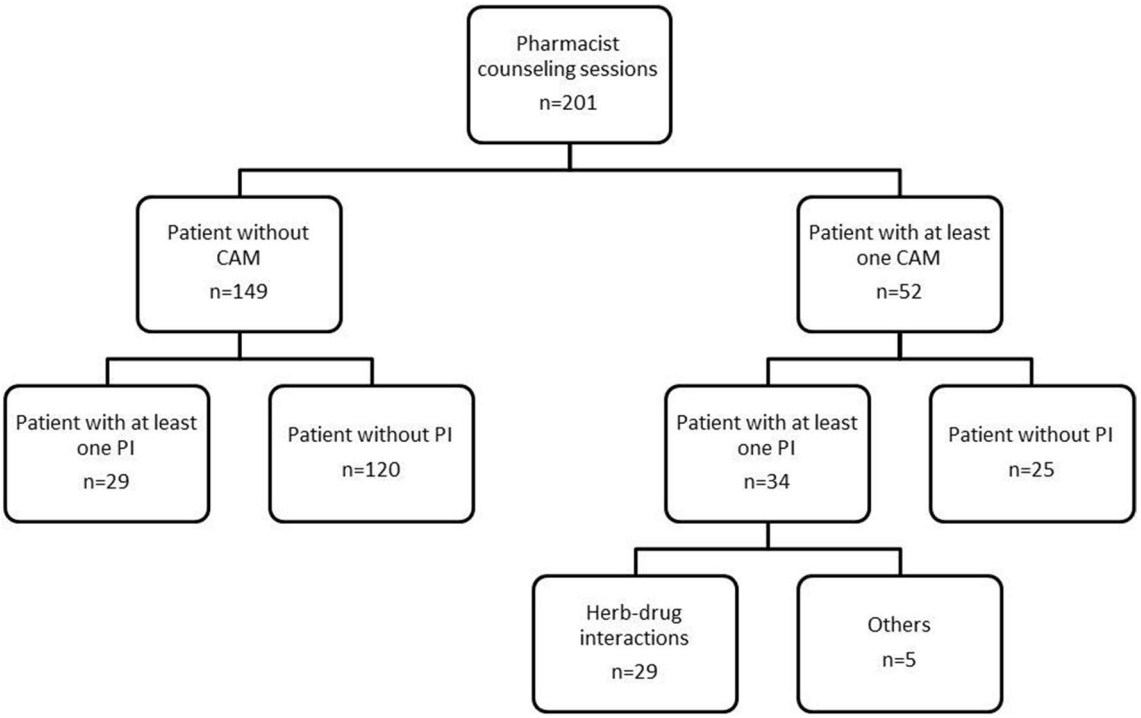

Fig. 1 Complementary and alternative medicines use and pharmaceutical interventions. *CAM* Complementary and alternative medicines, *PI* Pharmaceutical intervention

Table 2 Herb–drug interactions in patients with oral anticancer agents and pharmaceutical counseling sessions

	Oral antineoplastic agent	Plant
Contraindications: increase in antineoplastic agent concentrations	Capecitabine	Cannabis, German chamomile, grape seed, ginkgo, milk thistle, red yeast rice
	Erlotinib	Hibiscus, red yeast rice, thyme
	Everolimus	Red yeast rice, valerian
	Gefitinib	Aloe vera, dandelion, ginkgo, hibiscus, peppermint
	Palbociclib	Curcumin, mistletoe, peppermint, rosemary, thyme, verbena
	Pazopanib	Aloe vera, German chamomile, mistletoe
	Sorafenib	Grape seed
	Sunitinib	Aloe vera, hawthorn, thyme, verbena
Contraindications: decrease in antineoplastic agent concentrations	Everolimus	Hawthorn
	Gefitinib	Caraway seed
Precaution for use: same pharmacokinetic (OAA and plants inhibit or induce the same CYP or transporter)	Abiraterone	Verbena
	Afatinib	Pineapple
	Capecitabine	Curcumin, Echinacea
	Enzalutamide	Curcumin, dandelion, pineapple
	Erlotinib	Salpan
	Palbociclib	Corossol
Precaution for use: decrease of antineoplastic agent concentrations	Erlotinib	Fermented wheat germ extract, Psyllium
	Everolimus	Fermented wheat germ extract
	Gefitinib	Sweet cumin
	Sorafenib	Fermented wheat germ extract
Precaution for use: same side effects	Erlotinib	Psyllium, red yeast rice

CYP Cytochrome P450, *OAA* oral anticancer agent

Table 3 Enzymatic metabolism involved in oral anticancer agents

		CYP/UGT/SULT					
		Substrate		Inducer		Inhibitor	
	Bibliography	in vivo	in vitro	in vivo	in vitro	in vivo	in vitro
ABIRATERONE	[30–33]	CYP3A4 (inducer only)	–	–	–	CYP2D6 CYP2C8	–
AFATINIB	[30, 34–39]	*(CYP3A4)*	–	–	–	–	*(CYP1A2)* *(CYP2B6)* *(CYP2C8)* *(CYP2C9)* *(CYP2C19)* *(CYP2D6)* *(CYP3A4)* *(UGT2B7)*
AXITINIB[a]	[30, 40–43]	–	CYP3A4 CYP3A5 *(CYP1A2)* *(CYP2C19)* *(UGT1A1)*	–	–	–	–
CABOZANTINIB	[30, 44–46]	CYP3A4	*(CYP2C9)*	–	–	–	–
CAPECITABINE	[30, 47]	CYP2C9 DPD	–	–	–	CYP2C9	*(CYP1A2)* *(CYP3A4)* *(CYP2D6)*
COBIMETINIB	[30, 48–50]	CYP3A UGT2B7	–	–	CYP1A2	–	–
CRIZOTINIB	[30, 51–57]	–	CYP3A4 CYP3A5	–	CYP2B6 (PXR) CYP2C8 (PXR) CYP2C9 (PXR) UGT1A1 (PXR)	CYP3A4 CYP2B6	CYP3A4 CYP2B6 *(UGT1A1)* *(UGT2B7)*
CYCLOPHOSPHAMIDE	[30, 58–61]	–	CYP2A6 CYP2B6 CYP3A4 CYP3A5 CYP2C9 CYP2C18 CYP2C19	–	–	–	–
DABRAFENIB	[30, 62–64]	CYP2C8 CYP3A4	–	CYP2C8 CYP2C9 CYP2C19	CYP3A CYP2B6 UGT	–	CYP3A4 *(CYP2C9)*
ENZALUTAMIDE	[30, 65–67]	CYP2C8 (inhibitor only) *(CYP3A4)* *(CYP3A5)*	–	CYP3A UGT1A1 *(CYP2B6)* *(CYP2C9)* *(CYP2C19)*	*(CYP1A1)* *(CYP1A2)* *(CYP3A5)* *(UGT1A3)* *(UGT1A9)*	–	–
ERLOTINIB	[30, 68–71]	CYP3A4 *(CYP1A2)* *(CYP1A1)* *(CYP1B1)*	CYP3A5	–	–	–	CYP1A1 UGT1A1 CYP2C8 *(CYP3A4)*
ETOPOSIDE	[30, 72, 73]	CYP3A4	–	–	CYP3A4 CYP2C9	–	–
EVEROLIMUS	[12, 30, 74–78]	–	CYP3A4 CYP3A5 *(CYP2C8)*	–	–	–	CYP3A4 CYP2D6
GEFITINIB	[30, 57, 70, 79–83]	–	CYP3A4 CYP3A5 CYP1A1 CYP2D6	–	–	–	*(CYP2D6)*
IMATINIB[a]	[30, 65, 84–90]	–	CYP3A4 CYP3A5 CYP2C8 (auto inhibition)	–	–	–	CYP2C9 CYP3A4 CYP3A5 *(CYP2D6)*

Table 3 (continued)

		CYP/UGT/SULT					
		Substrate		Inducer		Inhibitor	
	Bibliography	in vivo	in vitro	in vivo	in vitro	in vivo	in vitro
LAPATINIB[a]	[30, 91–95]	–	CYP3A4 CYP3A5 *(CYP2C19)* *(CYP2C8)*	–	–	–	CYP3A CYP2C8
LENVATINIB	[30, 96, 97]	–	*(CYP3A4)*	–	–	–	–
LOMUSTINE	[30]	–	–	–	–	*(CYP3A4)*	–
OLAPARIB	[30, 98–100]	CYP3A4 CYP3A5	–	–	*(CYP3A)* *(CYP1A2)* *CYP2B6)* *(CYP2C9)* *(CYP2C19)*	–	*(CYP3A4)* *(CYP3A5)*
OSIMERTINIB	[30, 101–105]	–	CYP3A4 (inducer only) CYP3A5	–	–	–	–
PALBOCICLIB	[30, 106–108]	CYP3A SULT2A1	–	–	–	CYP3A	–
PAZOPANIB[a]	[30, 109–114]	CYP3A4 *(CYP1A2)* *(CYP2C8)*	–	–	–	–	CYP1A2 CYP3A4 CYP2B6 CYP2D6 CYP2C8 CYP2C9 CYP2C19 CYP2E1 UGT1A1
REGORAFENIB	[30, 115–119]	–	CYP3A4 *(UGT1A9)*	–	–	–	UGT1A1 UGT1A9
SORAFENIB	[30, 87, 120–122]	–	CYP3A4 (inducer only) UGT1A9	–	–	–	*(CYP2B6)* *(CYP2C8)* *(CYP2C9)* UGT1A1 UGT1A9
SUNITINIB[a]	[30, 79, 111, 123–126]	–	CYP3A4 CYP1A2	–	–	–	CYP3A4
TEMOZOLOMIDE	[30, 127]	–	–	–	–	–	–
TRAMETINIB	[30, 128–130]	–	–	–	–	–	–
VANDETANIB	[30, 114, 131–135]	–	CYP3A4 (inducer only) FMO1 FMO3	–	–	–	–
VEMURAFENIB	[30, 136–139]	–	CYP3A4 UGT	–	CYP3A4 CYP2B6 CYP2C8	–	CYP1A2
VINORELBINE	[30, 140–147]	–	CYP3A4	–	–	–	–
VISMODEGIB	[30, 148, 149]	–	CYP3A4 (inducer only)	–	–	–	–

Strong-Moderate-Major/(*Weakly*)-(*Minor*)

BCRP Breast cancer resistance protein, *CYP* Cytochrom P450, *DPD* Dihydropyrimidine dehydrogenase, *MATE* Multi-antimicrobial extrusion protein, *MRP* Multidrug resistance-associated protein, *OAT* Organic anion transporter, *OATP* Organic-anion-transporting polypeptide, *OCT* Organic cation transport, *P-gp* P-glycoprotein, *UGT* Uridine diphosphate-glucuronosyltransferase

[a]Discrepancies between studies

Table 4 Transporters involved in oral anticancer agents

		Transporter					
		Substrate		Inducer		Inhibitor	
	Bibliography	in vivo	in vitro	in vivo	in vitro	in vivo	in vitro
ABIRATERONE	[30–33]	–	–	–	–	–	OATP1B1
AFATINIB	[30, 34–39]	–	P-gp BCRP	–	–	–	*(P-gp)* *BCRP* *(OATP1B1)* *(OATP1B3)* *(OAT1)* *(OAT3)* *(OCT2)*
AXITINIB[a]	[30, 40–43]	–	–	–	–	–	*(P-gp)* *(BCRP)*
CABOZANTINIB	[30, 44–46]	–	MRP2	–	–	–	P-gp
CAPECITABINE	[30, 47]	–	–	–	–	–	–
COBIMETINIB	[30, 48–50]	P-gp	–	–	–	–	*(OATP1B1)* *(OTAP1B3)* *(OCT1)* *(BCRP)*
CRIZOTINIB	[30, 51–57]	–	P-gp	–	–	–	P-gp OCT1 OCT2 MATE 1
CYCLOPHOSPHAMIDE	[30, 58–61]	–	–	–	–	–	–
DABRAFENIB	[30, 62–64]	*(P-gp)* *(BCRP)*	–	MRP2	P-gp	BCRP OATP1B1 OATP1B3	*(OAT1)* *(OAT3)* *((OCT2)* *(OATP4C1)*
ENZALUTAMIDE	[30, 65–67]	–	–	P-gp MRP2 BCRP OATP1B1	–	–	P-gp *(BCRP)* *(OAT3)* *(OCT1)* *(MRP2)* *(OATP)*
ERLOTINIB	[30, 68–71]	–	P-gp	–	–	–	–
ETOPOSIDE	[30, 72, 73]	–	*(P-gp)*	–	–	–	–
EVEROLIMUS	[12, 30, 74–78]	–	P-gp	–	–	–	*(P-gp)* *(BCRP)*
GEFITINIB	[30, 57, 70, 79–83]	–	P-gp	–	*(OATP1B3)*	–	OAT1B1 OATP2B1 OCT2 MATE 1 *(OATP4C1)* *(BCRP)*
IMATINIB[a]	[30, 65, 84–90]	–	MDR	–	–	–	(*OATP4C1*) MATE1 OCT2
LAPATINIB[a]	[30, 91–95]	–	P-gp BCRP	–	–	–	P-gp *(BCRP)* *(OATP1B1)*
LENVATINIB	[30, 96, 97]	–	P-gp BCRP	–	–	–	–
LOMUSTINE	[30]	–	–	–	–	–	–

Table 4 (continued)

		Transporter					
		Substrate		Inducer		Inhibitor	
	Bibliography	in vivo	in vitro	in vivo	in vitro	in vivo	in vitro
OLAPARIB	[30, 98–100]	–	P-gp	–	*(P-gp)*	–	P-gp *(BCRP)* *(OATP1B1)* *(OCT1)* *(OCT2)* *(OCT3)* *(MATE 1)* *(MATE 2K)*
OSIMERTINIB	[30, 101–105]	–	–	–	–	–	BCRP P-gp
PALBOCICLIB	[30, 106–108]	–	–	–	–	–	P-gp BCRP OCT2 *(OCT1)* *(OAT3)* *OATP1B1)* *(OATP1B3)* *(BSEP)*
PAZOPANIB[a]	[30, 109–114]	–	P-gp BCRP OCT 1	–	–	–	OATP1B MATE 1 P-gp OCT 2 MAT2K
REGORAFENIB	[30, 115–119]	–	P-gp BCRP (metabolites) MRP2OATP1B1	–	–	–	BCRP P-gp
SORAFENIB	[30, 87, 120–122]	–	OATP1B1 OATP1B3	–	–	–	P-gp OCT2 MATE 1
SUNITINIB[a]	[30, 79, 111, 123–126]	BCRP	*(P-gp)*	–	–	–	MATE 1 OCT2
TEMOZOLOMIDE	[30, 127]	–	–	–	–	–	–
TRAMETINIB	[30, 128–130]	P-gp	BCRP	–	–	–	BCRP P-gp
VANDETANIB	[30, 114, 131–135]	–	P-gp	–	–	–	P-gp OCT2 OATP1B3
VEMURAFENIB	[30, 136–139]	–	P-gp BCRP	–	–	–	P-gp BCRP
VINORELBINE	[30, 140–147]	–	*(P-gp)*	–	–	–	–
VISMODEGIB	[30, 148, 149]	–	–	–	–	–	BCRP OATP1B1

Strong-Moderate-Major/(*Weakly*)-(*Minor*)

BCRP Breast cancer resistance protein, *CYP* Cytochrom P450, *DPD* Dihydropyrimidine dehydrogenase, *MATE* Multi-antimicrobial extrusion protein, *MRP* Multidrug resistance-associated protein, *OAT* Organic anion transporter, *OATP* Organic-anion-transporting polypeptide, *OCT* Organic cation transport, *P-gp* P-glycoprotein, *UGT* Uridine diphosphate-glucuronosyltransferase

[a]Discrepancies between studies

According to the systematic review, the Supplementary material presents the matches between 73 medicinal plants and 31 OAA [20–23, 73, 74, 150–276].

A total of 1829 recommendations were formulated about 59 (81.9%) medical plants and their interaction with an OAA (double entry table available in supplementary material). For 18.1 percent of them ($n=13$), no publications were found:

Acerola (*Malpighia sp.*); Albizia (*Albizia sp.*); Black horehound (*Ballota nigra*); Blackcurrant (*Ribes nigrum*); Chaenomeles Fruit (*Chaenomelis sp.*); Lemon balm (*Melissa officinalis*); Linden (*Tilia vulgaris*); Oats (*Avena sativa*); Plantago (*Plantago asiatica L.*); Prickly pear (*Ficus carica*); Rauwolfia (*Rauvolfia sp.*); Szechuan lovage (*Ligusticum wallichii*); White dead nettle (*Lamium album*); Witch hazel (*Hamamelis Virginia*).

Almost every medicinal plant interacts with at least one OAA, except Meadowsweet (*Filipendula ulmaria*) and African plum tree (*Pygeum africanum*) [150].

Gentianae sp. had interactions with CYP450, but no specified isoform were found in literature [277].

Psyllium (*Plantago ovate)*, flax seed (*Linum sp.*); passion flower (*Passiflora)* and fermented wheat germ extract (*Triticum sp.*) had no metabolism interactions with OAA but decreased the absorption of OAA and should not be use concomitantly with OAA [21, 150, 153, 162, 172, 278, 279].

Amygdalin (*Prunus armeniaca)* and Pereiroá (*Pao Pereira*) had no metabolism interactions with OAA but can be toxic and life-threatening (unknown mechanism) [279, 280]. So it should not be used with an OAA. Precaution should be considered with sweet cumin or aniseed (*Pimpinella anisum*) because interactions with unknown mechanism were described [150, 281, 282].

Discussion and conclusion

In our daily practice study, pharmaceutical counseling sessions reduce the risk of interactions and optimize treatment. Indeed, through pharmaceutical counseling, drug-drug or herb–drug interactions are detected in more than 25% of all prescriptions. This result is the same as that found in the literature [8, 9].

In daily practice in the Besançon university hospital setting, CAM are used by 27.0% of the patients. More than 80 kinds of CAM are involved, most of which are herbs, but patients also take minerals or vitamins. Thus, their use is quite common, and we find the same tendency in the literature. In patients treated with OAA, the prevalence of CAM use varied between 17 and 84% and the use of phytotherapy between 19 and 40% [283–288]. The use of CAM and especially phytotherapy can be explained by the fact that plants and CAM are often thought to have anticancer virtues and are frequently encountered in this type of population. For example, blue-green algae, bromelain, curcumin, devil's claw, amygdalin, propolis, etc. are known for cancer chemoprevention and treatment [150, 185, 186, 217, 289–299].

The rate of herb–OAA interaction is 8% (4.3–11.8) (16 prescriptions for 201 patients receiving pharmaceutical counseling). More than one-third of patients taking a medicinal herbal treatment were at risk of an herb–drug interaction. This herb–drug interaction can lead to a potential clinical impact: it may decrease the efficacy or increase the toxicity of OAA [300]. Therefore, it is absolutely essential to provide this information to healthcare professionals in order to avoid the risk of toxicity or treatment inefficacy [204, 301]. Yet, in our study as in the literature, very few patients actually inform their caregivers (physician especially) [283].

Our systematic review has allowed us to create an exhaustive database based on daily practice to help pharmacists to identify HDI and adapt their counseling accordingly. When an interaction with a medicinal plant is described in literature for metabolism and/or transport, we consider that the plant should be avoided even there is only case report or in vitro studies.

There were limits to completeness. Firstly, data published in the literature for some HDI can be contradictory or describe only in vitro. Thus, for instance, for milk thistle, three studies describe a CYP3A4 inhibition [163, 219, 302, 303]. But Kawaguchi-Suzuki et al. report no significant inhibitory or inductive effects on major hepatic P450 enzymes [242]. Another example is grape seed extract: Etheridge et al. explain the inhibition effect of grape seed on CYP3A4, whereas Raucy et al. report that grape seed produced an increase in hepatocyte CYP3A4 mRNA ranging from 200 to 400% [150, 218, 219, 304]. Same results have been observed with Echinacea: Gurley BJ et al. describe an induction of CYP3A4 and CYP2A1 whereas Gorski et al. an inhibition [202, 206]. The explanation of these discrepancies may be a difference of dose or concentrations used in in vitro tests. The use of different part of plants (leaves or roots for example) could also influence the results of pharmacokinetic assay. Different commercial preparations of ginseng can give different inhibition or inductions according to the brand of manufacture [305]. Only few in vivo studies are available to describe the interaction between OAA and plants. Per example, one study reports the effect of St john's wort (*Hypericum perforatum*) on imatinib pharmacokinetics. St John's wort increases imatinib clearance and decreases the area under the curve (AUC). Thus, concomitant use of enzyme inducers, including St john's wort, may require a larger dose of imatinib to maintain clinical effectiveness [153, 186, 207, 230, 231, 267, 272, 273]. For some plants, only case reports are found to describe the interaction with an OAA [73]. For instance, a case reports an interaction between hibiscus (*Hibiscus sabdariffa*) and erlotinib in a woman treated by erlotinib for 5 years without any side effect. Suddenly she developed a severe cutaneous adverse effect on account of daily self-administration of tea made of hibiscus flowers, with inhibition of CYP3A4 and CYP1A1 [237]. Another case reports liver toxicity due to interaction between Chinese herb and temozolomide [127]. Thus, medicinal plants should be used with caution with this drug.

Second, for many plants, the anticancer activity has not been assessed in humans. Their efficacy and the safety of

combining them with anticancer drugs have not been studied. In addition, the number of clinically relevant HDI is probably under-reported. Therefore, cancer and concomitant use of some CAM should be avoided. This study could be developed further to include alternative plants, replacing those that must be avoided.

Thirdly, only pharmacokinetic interactions were analyzed. Pharmacodynamic interactions, like addition of anticoagulant effect or hypokalemia, were not taken into account [306].

For some plants, no data are available. In daily practice, we advise the patient to stop the consumption of these plants.

In conclusion, this study confirmed that HDI should not be ignored by healthcare providers in their management of cancer patients in daily practice [307]. They must inquire about patients' use of CAM and adapt their counseling accordingly. The tool we have created can be used during pharmaceutical counseling sessions and be proposed to community and hospital pharmacists as well as other healthcare providers in our region. The tool allows us to summarize the interactions between 72 plants and 31 OAA. Some health institutions have created databases about this subject. But, in the one hand, there is a granted access and in the other hand, the data are not exhaustive [186, 308, 309]. Analyzing the HDI in daily practice is both quick and efficient. This tool will be supplemented by other OAA used in oncology and alternative herbs.

Compliance with ethical standards

Conflict of interest All authors declared that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments. In France, this search is considered like a non-interventional study according to European legislation and only a declaration to the CNIL (French data protection authority) is required: authorization granted number 1907874. All patients were individually informed that their data should be used to scientific research.

References

1. Maher RL, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13:57–65. https://doi.org/10.1517/14740338.2013.827660.
2. Voll ML, Yap KD, Terpstra WE, et al. Potential drug-drug interactions between anti-cancer agents and community pharmacy dispensed drugs. Pharm World Sci. 2010;32:575–80.
3. Van Leeuwen RWF, Jansman FGA, van den Bemt PMLA, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015;26:992–7.
4. van Leeuwen RWF, van Gelder T, Mathijssen RHJ, et al. Drug–drug interactions with tyrosine-kinase inhibitors: a clinical perspective. Lancet Oncol. 2014;15:e315–26.
5. Van Leeuwen RWF, Brundel DHS, Neef C, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013;108:1071–8.
6. Girre V, Arkoub H, Puts MTE, et al. Potential drug interactions in elderly cancer patients. Crit Rev Oncol/Hematol. 2011;78:220–6.
7. Beijnen JH, Schellens JH. Drug interactions in oncology. Lancet Oncol. 2004;5:489–96.
8. Scripture CD, Figg WD. Drug interactions in cancer therapy. Nat Rev Cancer. 2006;6:546–58.
9. Hadjibabaie M, Badri S, Ataei S, et al. Potential drug-drug interactions at a referral hematology-oncology ward in Iran: a cross-sectional study. Cancer Chemother Pharmacol. 2013;71:1619–27.
10. Tanaka E. Clinically important pharmacokinetic drug-drug interactions: role of cytochrome P450 enzymes. J Clin Pharm Ther. 1998;23:403–16.
11. Segal EM, Flood MR, Mancini RS, et al. Oral chemotherapy food and drug interactions: a comprehensive review of the literature. J Oncol Pract. 2014;10:e255–68.
12. Thomas-Schoemann A, Blanchet B, Bardin C, et al. Drug interactions with solid tumour-targeted therapies. Crit Rev Oncol Hematol. 2014;89:179–96.
13. Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? Ann Oncol. 2009;20:1907–12.
14. WHO| Traditional Complementary Integrative Medicine. WHO, http://www.who.int/traditional-complementary-integrative-medicine/about/en/. Accessed 14 April 2018.
15. Guide qualite de la prise en charge medicamenteuse, http://social-sante.gouv.fr/IMG/pdf/Guide_qualite_de_la_prise_en_charge_medicamenteuse.pdf Accessed 27 April 2017.
16. Vincent L., Giraudier F., Le Rat P., et al. Cytotoxiques oraux : Risques iatrogènes ?—Groupe d'Evaluation et de Recherche sur la Protection en Atmosphère Contrôlée (GERPAC), http://www.gerpac.eu/spip.php?article32. 2010, Accessed 27 April 2017.
17. Horneber M, Bueschel G, Dennert G, et al. How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. Integr Cancer Ther. 2012;11:187–203.
18. Richardson MA, Sanders T, Palmer JL, et al. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. JCO. 2000;18:2505–14.
19. Ernst E. How the public is being misled about complementary/alternative medicine. J R Soc Med. 2008;101:528–30.
20. Sparreboom A, Cox MC, Acharya MR, et al. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J Clin Oncol. 2004;22:2489–503.
21. Izzo AA. Interactions between herbs and conventional drugs: overview of the clinical data. Med Princ Pract. 2012;21:404–28.
22. Posadzki P, Watson L, Ernst E. Herb–drug interactions: an overview of systematic reviews. Br J Clin Pharmacol. 2013;75:603–18.
23. Gouws C, Steyn D, Plessis LD, et al. Combination therapy of Western drugs and herbal medicines: recent advances in understanding interactions involving metabolism and efflux. Exp Opin Drug Metab Toxicol. 2012;8:973–84.
24. Ben-Arye E, Samuels N, Goldstein LH, et al. Potential risks associated with traditional herbal medicine use in cancer care: a study of Middle Eastern oncology health care professionals. Cancer. 2016;122:598–610.
25. Conde-Estévez D, Albanell J. Oral chemotherapy prescription safety practices in Europe. Int J Clin Pharm. 2014;36:863–4.
26. Lopez-Martin C, Garrido Siles M, Alcaide-Garcia J, et al. Role of clinical pharmacists to prevent drug interactions in cancer outpatients: a single-centre experience. Int J Clin Pharm. 2014;36:1251–9.

27. Bourmaud A, Pacaut C, Melis A, et al. Is oral chemotherapy prescription safe for patients? A cross-sectional survey. Ann Oncol. 2014;25:500–4.
28. Conde-Estévez D, Salas E, Albanell J. Survey of oral chemotherapy safety and adherence practices of hospitals in Spain. Int J Clin Pharm. 2013;35:1236–44.
29. Allenet B, Bedouch P, Rose F-X, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006;28:181–8.
30. European Medicines Agency, https://www.ema.europa.eu/. Accessed 1 Jan 2019.
31. Deb S, Chin MY, Adomat H, et al. Abiraterone inhibits 1α,25-dihydroxyvitamin D3 metabolism by CYP3A4 in human liver and intestine in vitro. J Steroid Biochem Mol Biol. 2014;144(Pt A):50–8.
32. Monbaliu J, Gonzalez M, Bernard A, et al. In vitro and in vivo drug-drug interaction studies to assess the effect of abiraterone acetate, abiraterone, and metabolites of abiraterone on CYP2C8 activity. Drug Metab Dispos. 2016;44:1682–91.
33. Bernard A, Vaccaro N, Acharya M, et al. Impact on abiraterone pharmacokinetics and safety: open-label drug-drug interaction studies with ketoconazole and rifampicin. Clin Pharmacol Drug Dev. 2015;4:63–73.
34. Wind S, Giessmann T, Jungnik A, et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. Clin Drug Investig. 2014;34:173–82.
35. Wind S, Schnell D, Ebner T, et al. Clinical pharmacokinetics and pharmacodynamics of afatinib. Clin Pharmacokinet. 2017;56:235–50.
36. Zhang Y, Wang C, Liu Z, et al. P-gp is involved in the intestinal absorption and biliary excretion of afatinib in vitro and in rats. Pharmacol Rep. 2018;70:243–50.
37. Koide H, Tsujimoto M, Takeuchi A, et al. Substrate-dependent effects of molecular-targeted anticancer agents on activity of organic anion transporting polypeptide 1B1. Xenobiotica. 2018;48:1059–71.
38. Stopfer P, Marzin K, Narjes H, et al. Afatinib pharmacokinetics and metabolism after oral administration to healthy male volunteers. Cancer Chemother Pharmacol. 2012;69:1051–61.
39. Schnell D, Buschke S, Fuchs H, et al. Pharmacokinetics of afatinib in subjects with mild or moderate hepatic impairment. Cancer Chemother Pharmacol. 2014;74:267–75.
40. Chen Y, Tortorici MA, Garrett M, et al. Clinical pharmacology of axitinib. Clin Pharmacokinet. 2013;52:713–25.
41. Gu R, Hibbs DE, Ong JA, et al. The multikinase inhibitor axitinib is a potent inhibitor of human CYP1A2. Biochem Pharmacol. 2014;88:245–52.
42. Reyner EL, Sevidal S, West MA, et al. In vitro characterization of axitinib interactions with human efflux and hepatic uptake transporters: implications for disposition and drug interactions. Drug Metab Dispos. 2013;41:1575–83.
43. Zientek MA, Goosen TC, Tseng E, et al. In vitro kinetic characterization of axitinib metabolism. Drug Metab Dispos. 2016;44:102–14.
44. Nguyen L, Holland J, Miles D, et al. Pharmacokinetic (PK) drug interaction studies of cabozantinib: effect of CYP3A inducer rifampin and inhibitor ketoconazole on cabozantinib plasma PK and effect of cabozantinib on CYP2C8 probe substrate rosiglitazone plasma PK. J Clin Pharmacol. 2015;55:1012–23.
45. Lacy S, Hsu B, Miles D, et al. Metabolism and disposition of cabozantinib in healthy male volunteers and pharmacologic characterization of its major metabolites. Drug Metab Dispos. 2015;43:1190–207.
46. Lacy SA, Miles DR, Nguyen LT. Clinical pharmacokinetics and pharmacodynamics of cabozantinib. Clin Pharmacokinet. 2017;56:477–91.
47. Miyazaki S, Satoh H, Ikenishi M, et al. Pharmacokinetic model analysis of interaction between phenytoin and capecitabine. Int J Clin Pharmacol Ther. 2016;54:657–65.
48. Budha NR, Ji T, Musib L, et al. Evaluation of cytochrome P450 3A4-Mediated drug-drug interaction potential for cobimetinib using physiologically based pharmacokinetic modeling and simulation. Clin Pharmacokinet. 2016;55:1435–45.
49. Choo EF, Ly J, Chan J, et al. Role of P-glycoprotein on the brain penetration and brain pharmacodynamic activity of the MEK inhibitor cobimetinib. Mol Pharm. 2014;11:4199–207.
50. Choo EF, Woolsey S, DeMent K, et al. Use of transgenic mouse models to understand the oral disposition and drug-drug interaction potential of cobimetinib, a MEK inhibitor. Drug Metab Dispos. 2015;43:864–9.
51. Arakawa H, Omote S, Tamai I. Inhibitory Effect of Crizotinib on Creatinine Uptake by Renal Secretory Transporter OCT2. J Pharm Sci. 2017;106:2899–903.
52. Sato T, Mishima E, Mano N, et al. Potential drug interactions mediated by renal organic anion transporter OATP4C1. J Pharmacol Exp Ther. 2017;362:271–7.
53. Yamazaki S, Johnson TR, Smith BJ. Prediction of drug–drug interactions with crizotinib as the CYP3A substrate using a physiologically based pharmacokinetic model. Drug Metab Dispos. 2015;43:1417–29.
54. Hamilton G, Rath B, Burghuber O. Pharmacokinetics of crizotinib in NSCLC patients. Expert Opin Drug Metab Toxicol. 2015;11:835–42.
55. Xu H, O'Gorman M, Tan W, et al. The effects of ketoconazole and rifampin on the single-dose pharmacokinetics of crizotinib in healthy subjects. Eur J Clin Pharmacol. 2015;71:1441–9.
56. Mao J, Johnson TR, Shen Z, et al. Prediction of crizotinib-midazolam interaction using the Simcyp population-based simulator: comparison of CYP3A time-dependent inhibition between human liver microsomes versus hepatocytes. Drug Metab Dispos. 2013;41:343–52.
57. Sato T, Ito H, Hirata A, et al. Interactions of crizotinib and gefitinib with organic anion-transporting polypeptides (OATP)1B1, OATP1B3 and OATP2B1: gefitinib shows contradictory interaction with OATP1B3. Xenobiotica. 2018;48:73–8.
58. El-Serafi I, Afsharian P, Moshfegh A, et al. Cytochrome P450 Oxidoreductase Influences CYP2B6 Activity in Cyclophosphamide Bioactivation. PLoS ONE. 2015;10:e0141979.
59. Zhang X, Liu J, Ye F, et al. Effects of triptolide on the pharmacokinetics of cyclophosphamide in rats: a possible role of cytochrome P3A4 inhibition. Chin J Integr Med. 2014;20:534–9.
60. Park D, Yang Y-H, Choi E-K, et al. Licorice extract increases cyclophosphamide teratogenicity by upregulating the expression of cytochrome P-450 2B mRNA. Birth Defects Res B Dev Reprod Toxicol. 2011;92:553–9.
61. Yang L, Yan C, Zhang F, et al. Effects of ketoconazole on cyclophosphamide metabolism: evaluation of CYP3A4 inhibition effect using the in vitro and in vivo models. Exp Anim. 2018;67:71–82.
62. Ellens H, Johnson M, Lawrence SK, et al. Prediction of the transporter-mediated drug-drug interaction potential of dabrafenib and its major circulating metabolites. Drug Metab Dispos. 2017;45:646–56.
63. Puszkiel A, Noé G, Bellesoeur A, et al. Clinical pharmacokinetics and pharmacodynamics of dabrafenib. Clin Pharmacokinet. 2018. https://doi.org/10.1007/s40262-018-0703-0.

64. Suttle AB, Grossmann KF, Ouellet D, et al. Assessment of the drug interaction potential and single- and repeat-dose pharmacokinetics of the BRAF inhibitor dabrafenib. J Clin Pharmacol. 2015;55:392–400.
65. Gibbons JA, Ouatas T, Krauwinkel W, et al. Clinical pharmacokinetic studies of enzalutamide. Clin Pharmacokinet. 2015;54:1043–55.
66. Backman JT, Filppula AM, Niemi M, et al. Role of cytochrome P450 2C8 in drug metabolism and interactions. Pharmacol Rev. 2016;68:168–241.
67. Weiss J, Kocher J, Mueller C, et al. Impact of enzalutamide and its main metabolite N-desmethyl enzalutamide on pharmacokinetically important drug metabolizing enzymes and drug transporters. Biopharm Drug Dispos. 2017;38:517–25.
68. Hamilton M, Wolf JL, Drolet DW, et al. The effect of rifampicin, a prototypical CYP3A4 inducer, on erlotinib pharmacokinetics in healthy subjects. Cancer Chemother Pharmacol. 2014;73:613–21.
69. Calvert H, Twelves C, Ranson M, et al. Effect of erlotinib on CYP3A activity, evaluated in vitro and by dual probes in patients with cancer. Anticancer Drugs. 2014;25:832–40.
70. Li J, Zhao M, He P, et al. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res. 2007;13:3731–7.
71. Dong P, Fang Z, Zhang Y, et al. Substrate-dependent modulation of the catalytic activity of CYP3A by erlotinib. Acta Pharmacol Sin. 2011;32:399–407.
72. Song J-H, Sun D-X, Chen B, et al. Inhibition of CYP3A4 and CYP2C9 by podophyllotoxin: implication for clinical drug-drug interactions. J Biosci. 2011;36:879–85.
73. Bossaer JB, Odle BL. Probable etoposide interaction with *Echinacea*. J Diet Suppl. 2012;9:90–5.
74. Hsieh Y-W, Huang C-Y, Yang S-Y, et al. Oral intake of curcumin markedly activated CYP 3A4: in vivo and ex vivo studies. Sci Rep. 2014;4:6587.
75. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. Clin Pharmacokinet. 2004;43:83–95.
76. González F, Valjalo R. Combining cytochrome P-450 3A4 modulators and cyclosporine or everolimus in transplantation is successful. World J Transplant. 2015;5:338–47.
77. Ravaud A, Urva SR, Grosch K, et al. Relationship between everolimus exposure and safety and efficacy: meta-analysis of clinical trials in oncology. Eur J Cancer. 2014;50:486–95.
78. Tang SC, Sparidans RW, Cheung KL, et al. P-glycoprotein, CYP3A, and plasma carboxylesterase determine brain and blood disposition of the mTOR Inhibitor everolimus (Afinitor) in mice. Clin Cancer Res. 2014;20:3133–45.
79. Omote S, Matsuoka N, Arakawa H, et al. Effect of tyrosine kinase inhibitors on renal handling of creatinine by MATE1. Sci Rep. 2018;8:9237.
80. Han S-Y, Zhao H-Y, Zhou N, et al. Marsdenia tenacissima extract inhibits gefitinib metabolism in vitro by interfering with human hepatic CYP3A4 and CYP2D6 enzymes. J Ethnopharmacol. 2014;151:210–7.
81. Wang D-D, Liu Y, Li N, et al. Induction of CYP1A1 increases gefitinib-induced oxidative stress and apoptosis in A549 cells. Toxicol In Vitro. 2017;44:36–43.
82. Fang P, Zheng X, He J, et al. Functional characterization of wild-type and 24 CYP2D6 allelic variants on gefitinib metabolism in vitro. Drug Des Devel Ther. 2017;11:1283–90.
83. Zhao C, Han S-Y, Li P-P. Pharmacokinetics of gefitinib: roles of drug metabolizing enzymes and transporters. Curr Drug Deliv. 2017;14:282–8.
84. Harivenkatesh N, Kumar L, Bakhshi S, et al. Influence of MDR1 and CYP3A5 genetic polymorphisms on trough levels and therapeutic response of imatinib in newly diagnosed patients with chronic myeloid leukemia. Pharmacol Res. 2017;120:138–45.
85. Verboom MC, Visser L, Kouwen S, et al. Influence of CYP2C8 polymorphisms on imatinib steady-state trough level in chronic myeloid leukemia and gastrointestinal stromal tumor patients. Pharmacogenet Genomics. 2017;27:223–6.
86. Osorio S, Escudero-Vilaplana V, Gómez-Centurión I, et al. Inadequate response to imatinib treatment in chronic myeloid leukemia due to a drug interaction with phenytoin. J Oncol Pharm Pract. 2017;25:694–8.
87. Murray M, Gillani TB, Ghassabian S, et al. Differential effects of hepatic cirrhosis on the intrinsic clearances of sorafenib and imatinib by CYPs in human liver. Eur J Pharm Sci. 2018;114:55–63.
88. Skoglund K, Richter J, Olsson-Strömberg U, et al. In vivo cytochrome P450 3A isoenzyme activity and pharmacokinetics of imatinib in relation to therapeutic outcome in patients with chronic myeloid leukemia. Ther Drug Monit. 2016;38:230–8.
89. Filppula AM, Neuvonen M, Laitila J, et al. Autoinhibition of CYP3A4 leads to important role of CYP2C8 in imatinib metabolism: variability in CYP2C8 activity may alter plasma concentrations and response. Drug Metab Dispos. 2013;41:50–9.
90. Filppula AM, Tornio A, Niemi M, et al. Gemfibrozil impairs imatinib absorption and inhibits the CYP2C8-mediated formation of its main metabolite. Clin Pharmacol Ther. 2013;94:383–93.
91. Koch KM, Smith DA, Botbyl J, et al. Effect of lapatinib on oral digoxin absorption in patients. Clin Pharmacol Drug Dev. 2015;4:449–53.
92. Koch KM, Dees EC, Coker SA, et al. The effects of lapatinib on CYP3A metabolism of midazolam in patients with advanced cancer. Cancer Chemother Pharmacol. 2017;80:1141–6.
93. Hardy KD, Wahlin MD, Papageorgiou I, et al. Studies on the role of metabolic activation in tyrosine kinase inhibitor-dependent hepatotoxicity: induction of CYP3A4 enhances the cytotoxicity of lapatinib in HepaRG cells. Drug Metab Dispos. 2014;42:162–71.
94. Chan ECY, New LS, Chua TB, et al. Interaction of lapatinib with cytochrome P450 3A5. Drug Metab Dispos. 2012;40:1414–22.
95. Towles JK, Clark RN, Wahlin MD, et al. Cytochrome P450 3A4 and CYP3A5-Catalyzed Bioactivation of Lapatinib. Drug Metab Dispos. 2016;44:1584–97.
96. Gupta A, Jarzab B, Capdevila J, et al. Population pharmacokinetic analysis of lenvatinib in healthy subjects and patients with cancer. Br J Clin Pharmacol. 2016;81:1124–33.
97. Shumaker RC, Aluri J, Fan J, et al. Effect of rifampicin on the pharmacokinetics of lenvatinib in healthy adults. Clin Drug Investig. 2014;34:651–9.
98. Munroe M, Kolesar J. Olaparib for the treatment of BRCA-mutated advanced ovarian cancer. Am J Health Syst Pharm. 2016;73:1037–41.
99. Dirix L, Swaisland H, Verheul HMW, et al. Effect of itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two phase I open-label studies. Clin Ther. 2016;38:2286–99.
100. McCormick A, Swaisland H, Reddy VP, et al. In vitro evaluation of the inhibition and induction potential of olaparib, a potent poly(ADP-ribose) polymerase inhibitor, on cytochrome P450. Xenobiotica. 2018;48:555–64.
101. Pilla Reddy V, Walker M, Sharma P, et al. Development, verification, and prediction of osimertinib drug-drug interactions using pbpk modeling approach to inform drug label. CPT Pharmacometrics Syst Pharmacol. 2018;7:321–30.
102. Dickinson PA, Cantarini MV, Collier J, et al. Metabolic Disposition of osimertinib in rats, dogs, and humans: insights into a drug designed to bind covalently to a cysteine residue

of epidermal growth factor receptor. Drug Metab Dispos. 2016;44:1201–12.
103. Chen Z, Chen Y, Xu M, et al. Osimertinib (AZD9291) enhanced the efficacy of chemotherapeutic agents in ABCB1- and ABCG2-overexpressing cells in vitro, in vivo, and ex vivo. Mol Cancer Ther. 2016;15:1845–58.
104. Hsiao S-H, Lu Y-J, Li Y-Q, et al. Osimertinib (AZD9291) attenuates the function of multidrug resistance-linked atp-binding cassette transporter ABCB1 in vitro. Mol Pharm. 2016;13:2117–25.
105. Zhang X-Y, Zhang Y-K, Wang Y-J, et al. Osimertinib (AZD9291), a mutant-selective egfr inhibitor, reverses ABCB1-mediated drug resistance in cancer cells. Molecules. 2016;21:1236. https://doi.org/10.3390/molecules21091236.
106. Yu Y, Loi C-M, Hoffman J, et al. Physiologically based pharmacokinetic modeling of palbociclib. J Clin Pharmacol. 2017;57:173–84.
107. Pabla N, Gibson AA, Buege M, et al. Mitigation of acute kidney injury by cell-cycle inhibitors that suppress both CDK4/6 and OCT2 functions. Proc Natl Acad Sci USA. 2015;112:5231–6.
108. De Gooijer MC, Zhang P, Thota N, et al. P-glycoprotein and breast cancer resistance protein restrict the brain penetration of the CDK4/6 inhibitor palbociclib. Invest New Drugs. 2015;33:1012–9.
109. Wang Y-K, Yang X-N, Liang W-Q, et al. A metabolomic perspective of pazopanib-induced acute hepatotoxicity in mice. Xenobiotica. 2018. https://doi.org/10.1080/00498254.2018.1489167.
110. Liu X-J, Lu H, Sun J-X, et al. Metabolic behavior prediction of pazopanib by cytochrome P450 (CYP) 3A4 by molecular docking. Eur J Drug Metab Pharmacokinet. 2016;41:465–8.
111. Filppula AM, Neuvonen PJ, Backman JT. In vitro assessment of time-dependent inhibitory effects on CYP2C8 and CYP3A activity by fourteen protein kinase inhibitors. Drug Metab Dispos. 2014;42:1202–9.
112. Ellawatty WEA, Masuo Y, Fujita K-I, et al. Organic cation transporter 1 is responsible for hepatocellular uptake of the tyrosine kinase inhibitor pazopanib. Drug Metab Dispos. 2018;46:33–40.
113. Sauzay C, White-Koning M, Hennebelle I, et al. Inhibition of OCT2, MATE1 and MATE2-K as a possible mechanism of drug interaction between pazopanib and cisplatin. Pharmacol Res. 2016;110:89–95.
114. Khurana V, Minocha M, Pal D, et al. Inhibition of OATP-1B1 and OATP-1B3 by tyrosine kinase inhibitors. Drug Metabol Drug Interact. 2014;29:249–59.
115. Wang Y-J, Zhang Y-K, Zhang G-N, et al. Regorafenib overcomes chemotherapeutic multidrug resistance mediated by ABCB1 transporter in colorectal cancer: in vitro and in vivo study. Cancer Lett. 2017;396:145–54.
116. Ohya H, Shibayama Y, Ogura J, et al. Regorafenib is transported by the organic anion transporter 1B1 and the multidrug resistance protein 2. Biol Pharm Bull. 2015;38:582–6.
117. Kort A, Durmus S, Sparidans RW, et al. Brain and testis accumulation of regorafenib is restricted by breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1). Pharm Res. 2015;32:2205–16.
118. Wang Y-K, Xiao X-R, Xu K-P, et al. Metabolic profiling of the anti-tumor drug regorafenib in mice. J Pharm Biomed Anal. 2018;159:524–35.
119. Paech F, Mingard C, Grünig D, et al. Mechanisms of mitochondrial toxicity of the kinase inhibitors ponatinib, regorafenib and sorafenib in human hepatic HepG2 cells. Toxicology. 2018;395:34–44.
120. Di Gion P, Kanefendt F, Lindauer A, et al. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. Clin Pharmacokinet. 2011;50:551–603.
121. Zimmerman EI, Hu S, Roberts JL, et al. Contribution of OATP1B1 and OATP1B3 to the disposition of sorafenib and sorafenib-glucuronide. Clin Cancer Res. 2013;19:1458–66.
122. Ting C-T, Cheng Y-Y, Tsai T-H. Herb–drug interaction between the traditional hepatoprotective formulation and sorafenib on hepatotoxicity, histopathology and pharmacokinetics in rats. Molecules. 2017;22:1034. https://doi.org/10.3390/molecules22071034.
123. Amaya GM, Durandis R, Bourgeois DS, et al. Cytochromes P450 1A2 and 3A4 catalyze the metabolic activation of sunitinib. Chem Res Toxicol. 2018;31:570–84.
124. Teo YL, Wee HL, Chue XP, et al. Effect of the CYP3A5 and ABCB1 genotype on exposure, clinical response and manifestation of toxicities from sunitinib in Asian patients. Pharmacogenomics J. 2016;16:47–53.
125. Patel ND, Chakrabory K, Messmer G, et al. Severe sunitinib-induced myelosuppression in a patient with a CYP 3A4 polymorphism. J Oncol Pharm Pract. 2018;24:623–6.
126. Reustle A, Fisel P, Renner O, et al. Characterization of the breast cancer resistance protein (BCRP/ABCG2) in clear cell renal cell carcinoma. Int J Cancer. 2018;143:3181–93. https://doi.org/10.1002/ijc.31741.
127. Melchardt T, Magnes T, Weiss L, et al. Liver toxicity during temozolomide chemotherapy caused by Chinese herbs. BMC Complement Altern Med. 2014;14:115.
128. De Gooijer MC, Zhang P, Weijer R, et al. The impact of P-glycoprotein and breast cancer resistance protein on the brain pharmacokinetics and pharmacodynamics of a panel of MEK inhibitors. Int J Cancer. 2018;142:381–91.
129. Katayama K, Fujiwara C, Noguchi K, et al. RSK1 protects P-glycoprotein/ABCB1 against ubiquitin-proteasomal degradation by downregulating the ubiquitin-conjugating enzyme E2 R1. Sci Rep. 2016;6:36134.
130. Qiu J-G, Zhang Y-J, Li Y, et al. Trametinib modulates cancer multidrug resistance by targeting ABCB1 transporter. Oncotarget. 2015;6:15494–509.
131. Johansson S, Read J, Oliver S, et al. Pharmacokinetic evaluations of the co-administrations of vandetanib and metformin, digoxin, midazolam, omeprazole or ranitidine. Clin Pharmacokinet. 2014;53:837–47.
132. Jovelet C, Deroussent A, Broutin S, et al. Influence of the multidrug transporter P-glycoprotein on the intracellular pharmacokinetics of vandetanib. Eur J Drug Metab Pharmacokinet. 2013;38:149–57.
133. Harmsen S, Meijerman I, Maas-Bakker RF, et al. PXR-mediated P-glycoprotein induction by small molecule tyrosine kinase inhibitors. Eur J Pharm Sci. 2013;48:644–9.
134. Jovelet C, Bénard J, Forestier F, et al. Inhibition of P-glycoprotein functionality by vandetanib may reverse cancer cell resistance to doxorubicin. Eur J Pharm Sci. 2012;46:484–91.
135. Martin P, Oliver S, Robertson J, et al. Pharmacokinetic drug interactions with vandetanib during coadministration with rifampicin or itraconazole. Drugs R D. 2011;11:37–51.
136. MacLeod AK, McLaughlin LA, Henderson CJ, et al. Activation status of the pregnane X receptor influences vemurafenib availability in humanized mouse models. Cancer Res. 2015;75:4573–81.
137. Zhang W, Heinzmann D, Grippo JF. Clinical Pharmacokinetics of Vemurafenib. Clin Pharmacokinet. 2017;56:1033–43.
138. Durmus S, Sparidans RW, Wagenaar E, et al. Oral availability and brain penetration of the B-RAFV600E inhibitor vemurafenib can be enhanced by the P-GLYCOprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar. Mol Pharm. 2012;9:3236–45.
139. Mittapalli RK, Vaidhyanathan S, Sane R, et al. Impact of P-glycoprotein (ABCB1) and breast cancer resistance

protein (ABCG2) on the brain distribution of a novel BRAF inhibitor: vemurafenib (PLX4032). J Pharmacol Exp Ther. 2012;342:33–40.
140. Michaelis M, Rothweiler F, Wurglics M, et al. Substrate-specific effects of pirinixic acid derivatives on ABCB1-mediated drug transport. Oncotarget. 2016;7:11664–76.
141. Beulz-Riché D, Grudé P, Puozzo C, et al. Characterization of human cytochrome P450 isoenzymes involved in the metabolism of vinorelbine. Fundam Clin Pharmacol. 2005;19:545–53.
142. Topletz AR, Dennison JB, Barbuch RJ, et al. The relative contributions of CYP3A4 and CYP3A5 to the metabolism of vinorelbine. Drug Metab Dispos. 2013;41:1651–61.
143. Lagas JS, Damen CWN, van Waterschoot RAB, et al. P-glycoprotein, multidrug-resistance associated protein 2, Cyp3a, and carboxylesterase affect the oral availability and metabolism of vinorelbine. Mol Pharmacol. 2012;82:636–44.
144. Press RR, Buckle T, Beijnen JH, et al. The effect of P-glycoprotein and cytochrome P450 3a on the oral bioavailability of vinorelbine in mice. Cancer Chemother Pharmacol. 2006;57:819–25.
145. Sen S, Sharma H, Singh N. Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. Biochem Biophys Res Commun. 2005;331:1245–52.
146. Zhou XJ, Rahmani R. Preclinical and clinical pharmacology of vinca alkaloids. Drugs. 1992;44(Suppl 4):1–16 **discussion 66–69**.
147. Kajita J, Kuwabara T, Kobayashi H, et al. CYP3A4 is mainly responsibile for the metabolism of a new vinca alkaloid, vinorelbine, in human liver microsomes. Drug Metab Dispos. 2000;28:1121–7.
148. Abou-Alfa GK, Lewis LD, LoRusso P, et al. Pharmacokinetics and safety of vismodegib in patients with advanced solid malignancies and hepatic impairment. Cancer Chemother Pharmacol. 2017;80:29–36.
149. Malhi V, Colburn D, Williams SJ, et al. A clinical drug-drug interaction study to evaluate the effect of a proton-pump inhibitor, a combined P-glycoprotein/cytochrome 450 enzyme (CYP)3A4 inhibitor, and a CYP2C9 inhibitor on the pharmacokinetics of vismodegib. Cancer Chemother Pharmacol. 2016;78:41–9.
150. Williamson E, Driver S, Baxter K. Stockley's book herbal medicines interactions. 2009. https://www.stonybrookmedicine.edu/sites/default/files/herbal_medicines_interactions-1.pdf. Accessed 23 Sept 2018.
151. Chen S-H, Lin K-Y, Chang C-C, et al. Aloe-emodin-induced apoptosis in human gastric carcinoma cells. Food Chem Toxicol. 2007;45:2296–303.
152. Djuv A, Nilsen OG. Aloe vera juice: iC_{50} and dual mechanistic inhibition of CYP3A4 and CYP2D6. Phytother Res. 2012;26:445–51.
153. Vahabi S, Eatemadi A. Phyto-anesthetics: a mini-review on herb–anesthesia drug interactions. Biomed Pharmacother. 2016;84:1885–90.
154. Zhang Y, Huang L, Bi H, et al. Study of the upregulation of the activity of cytochrome P450 3A isoforms by Astragalus injection and Astragalus granules in rats and in cells. Eur J Drug Metab Pharmacokinet. 2013;38:105–13.
155. Or PMY, Lam FFY, Kwan YW, et al. Effects of Radix Astragali and Radix Rehmanniae, the components of an anti-diabetic foot ulcer herbal formula, on metabolism of model CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 probe substrates in pooled human liver microsomes and specific CYP isoforms. Phytomedicine. 2012;19:535–44.
156. Lau C, Mooiman KD, Maas-Bakker RF, et al. Effect of Chinese herbs on CYP3A4 activity and expression in vitro. J Ethnopharmacol. 2013;149:543–9.
157. He S-M, Yang A-K, Li X-T, et al. Effects of herbal products on the metabolism and transport of anticancer agents. Expert Opin Drug Metab Toxicol. 2010;6:1195–213.
158. Tian QE, De Li H, Yan M, et al. Effects of Astragalus polysaccharides on P-glycoprotein efflux pump function and protein expression in H22 hepatoma cells in vitro. BMC Complement Altern Med. 2012;12:94.
159. Pao LH, Hu OYP, Fan HY, et al. Herb–drug interaction of 50 Chinese herbal medicines on CYP3A4 activity in vitro and in vivo. Am J Chin Med. 2012;40:57–73.
160. Savranoglu S, Tumer TB. Inhibitory effects of spirulina platensis on carcinogen-activating cytochrome P450 isozymes and potential for drug interactions. Int J Toxicol. 2013;32:376–84.
161. Lu Y, Zhong H, Tang Q, et al. Construction and verification of CYP3A5 gene polymorphisms using a Saccharomyces cerevisiae expression system to predict drug metabolism. Mol Med Rep. 2017;15:1593–600.
162. Rahman H, Kim M, Leung G, et al. Drug–herb interactions in the elderly patient with IBD: a growing concern. Curr Treat Options Gastroenterol. 2017;15:618–36.
163. Sprouse AA, van Breemen RB. Pharmacokinetic interactions between drugs and botanical dietary supplements. Drug Metab Dispos. 2016;44:162–71.
164. Colombo D, Lunardon L, Bellia G. Cyclosporine and herbal supplement interactions. J Toxicol. 2014;2014:145325.
165. Arellano AL, Papaseit E, Romaguera A, et al. Neuropsychiatric and general interactions of natural and synthetic cannabinoids with drugs of abuse and medicines. CNS Neurol Disord Drug Targets. 2017;16:554–66. https://doi.org/10.2174/1871527316666170413104516.
166. Ashino T, Hakukawa K, Itoh Y, et al. Inhibitory effect of synthetic cannabinoids on CYP1A activity in mouse liver microsomes. J Toxicol Sci. 2014;39:815–20.
167. Kim JH, Kwon SS, Kong TY, et al. AM-2201 inhibits multiple cytochrome P450 and uridine 5'-diphospho-glucuronosyltransferase enzyme activities in human liver microsomes. Molecules. 2017;22:443. https://doi.org/10.3390/molecules22030443.
168. Kong TY, Kim J-H, Kwon S-S, et al. Inhibition of cytochrome P450 and uridine 5′-diphospho-glucuronosyltransferases by MAM-2201 in human liver microsomes. Arch Pharm Res. 2017;40:727–35.
169. Grabowsky JA. Drug interactions and the pharmacist: focus on everolimus. Ann Pharmacother. 2013;47:1055–63.
170. Dadkhah A, Allameh A, Khalafi H, et al. Inhibitory effects of dietary caraway essential oils on 1,2-dimethylhydrazine-induced colon carcinogenesis is mediated by liver xenobiotic metabolizing enzymes. Nutr Cancer. 2011;63:46–54.
171. Naderi-Kalali B, Allameh A, Rasaee MJ, et al. Suppressive effects of caraway (Carum carvi) extracts on 2, 3, 7, 8-tetrachloro-dibenzo-p-dioxin-dependent gene expression of cytochrome P450 1A1 in the rat H4IIE cells. Toxicol In Vitro. 2005;19:373–7.
172. Tarirai C, Viljoen AM, Hamman JH. Herb–drug pharmacokinetic interactions reviewed. Expert Opin Drug Metab Toxicol. 2010;6:1515–38.
173. Fujita K-I, Hidaka M, Takamura N, et al. Inhibitory effects of citrus fruits on cytochrome P450 3A (CYP3A) activity in humans. Biol Pharm Bull. 2003;26:1371–3.
174. Satoh H, Yamashita F, Tsujimoto M, et al. Citrus juices inhibit the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos. 2005;33:518–23.
175. Adeyemi DO, Komolafe OA, Adewole OS, et al. Anti hyperglycemic activities of Annona muricata (Linn). Afr J Tradit Complement Altern Med. 2008;6:62–9.
176. Fu L, He L, Liang Y, et al. Experimental chemotherapy against xenografts derived from multidrug resistant KBv200 cells and

parental drug-sensitive KB cells in nude mice by annonaceous acetogenin 89-2. Yao Xue Xue Bao. 2003;38:565–70.
177. Holanda CMDCX, Barbosa DA, Demeda VF, et al. Influence of Annona muricata (soursop) on biodistribution of radiopharmaceuticals in rats. Acta Cir Bras. 2014;29:145–50.
178. Scott IM, Leduc RI, Burt AJ, et al. The inhibition of human cytochrome P450 by ethanol extracts of North American botanicals. Pharma Biol. 2006;44:315–27.
179. Teksin ZS, Lee IJ, Nemieboka NN, et al. Evaluation of the transport, in vitro metabolism and pharmacokinetics of Salvinorin A, a potent hallucinogen. Eur J Pharm Biopharm. 2009;72:471–7.
180. Kim E, Sy-Cordero A, Graf TN, et al. Isolation and identification of intestinal CYP3A inhibitors from cranberry (Vaccinium macrocarpon) using human intestinal microsomes. Planta Med. 2011;77:265–70.
181. Dave AA, Samuel J. Suspected interaction of cranberry juice extracts and tacrolimus serum levels: a case report. Cureus. 2016;8:e610.
182. Srinivas NR. Cranberry juice ingestion and clinical drug-drug interaction potentials; review of case studies and perspectives. J Pharm Pharm Sci. 2013;16:289–303.
183. Mohamed MEF, Frye RF. Effects of herbal supplements on drug glucuronidation. Review of clinical, animal, and in vitro studies. Planta Med. 2011;77:311–21.
184. Foster B, Vandenhoek S, Hana J, et al. In vitro inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products. Phytomedicine. 2003;10:334–42.
185. Huet M. Medicinal plants in cancer patients: current practices and evaluation data. Bull Cancer. 2013;100:485–95.
186. Pourroy B, Letellier C, Helvig A, et al. Development of a rapid risk evaluation tool for herbs/drugs interactions in cancer patients: a multicentric experience in south of France. Eur J Cancer Care (Engl). 2017;1:1–10. https://doi.org/10.1111/ecc.12752.
187. Shamsi S, Chen Y, Lim LY. Characterization and biological properties of NanoCUR formulation and its effect on major human cytochrome P450 enzymes. Int J Pharm. 2015;495:194–203.
188. Cheng Y-Y, Hsieh C-H, Tsai T-H. Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics. J Food Drug Anal. 2018;26:S88–95.
189. Maliakal PP, Wanwimolruk S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol. 2001;53:1323–9.
190. Dufay S, Worsley A, Monteillier A, et al. Herbal tea extracts inhibit Cytochrome P450 3A4 in vitro. J Pharm Pharmacol. 2014;66:1478–90.
191. Calitz C, Steenekamp JH, Steyn JD, et al. Impact of traditional African medicine on drug metabolism and transport. Expert Opin Drug Metab Toxicol. 2014;10:991–1003.
192. Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. Rapid Commun Mass Spectrom. 2004;18:2273–81.
193. Romiti N, Tramonti G, Corti A, et al. Effects of Devil's Claw (Harpagophytum procumbens) on the multidrug transporter ABCB1/P-glycoprotein. Phytomedicine. 2009;16:1095–100.
194. Hostanska K, Melzer J, Rostock M, et al. Alteration of anti-inflammatory activity of Harpagophytum procumbens (devil's claw) extract after external metabolic activation with S9 mix. J Pharm Pharmacol. 2014;66:1606–14.
195. Okada N, Murakami A, Urushizaki S, et al. Extracts of immature orange (Aurantii fructus immaturus) and Citrus Unshiu Peel (Citri unshiu pericarpium) Induce P-Glycoprotein and Cytochrome P450 3A4 Expression via Upregulation of Pregnane X Receptor. Front Pharmacol. 2017;8:84.
196. Pandit S, Mukherjee PK, Ponnusankar S, et al. Metabolism mediated interaction of α-asarone and Acorus calamus with CYP3A4 and CYP2D6. Fitoterapia. 2011;82:369–74.
197. Hellum BH, Nilsen OG. In vitro inhibition of CYP3A4 metabolism and P-glycoprotein-mediated transport by trade herbal products. Basic Clin Pharmacol Toxicol. 2008;102:466–75.
198. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69:1777–98.
199. Budzinski JW, Foster BC, Vandenhoek S, et al. An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine. 2000;7:273–82.
200. Wanwimolruk S, Prachayasittikul V. Cytochrome P450 enzyme mediated herbal drug interactions (Part 1). EXCLI J. 2014;13:347–91.
201. Langhammer AJ, Nilsen OG. In vitro inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy. Phytother Res. 2014;28:603–10.
202. Gorski JC, Huang S-M, Pinto A, et al. The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 2004;75:89–100.
203. Liu R, Tam TW, Mao J, et al. The effect of natural health products and traditional medicines on the activity of human hepatic microsomal-mediated metabolism of oseltamivir. J Pharm Pharm Sci. 2010;13:43–55.
204. Awortwe C, Bouic PJ, Masimirembwa CM, et al. Inhibition of major drug metabolizing CYPs by common herbal medicines used by HIV/AIDS patients in Africa– implications for herb–drug interactions. Drug Metab Lett. 2014;7:83–95.
205. Hellum BH, Hu Z, Nilsen OG. Trade herbal products and induction of CYP2C19 and CYP2E1 in cultured human hepatocytes. Basic Clin Pharmacol Toxicol. 2009;105:58–63.
206. Gurley BJ, Swain A, Williams DK, et al. Gauging the clinical significance of P-glycoprotein-mediated herb–drug interactions: comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. Mol Nutr Food Res 2008;52:772–779.
207. Na DH, Ji HY, Park EJ, et al. Evaluation of metabolism-mediated herb–drug interactions. Arch Pharm Res. 2011;34:1829–42.
208. Haefeli WE, Carls A. Drug interactions with phytotherapeutics in oncology. Expert Opin Drug Metab Toxicol. 2014;10:359–77.
209. Nguyen S, Huang H, Foster BC, et al. Antimicrobial and P450 inhibitory properties of common functional foods. J Pharm Pharm Sci. 2014;17:254–65.
210. Subehan null, Zaidi SFH, Kadota S, et al. Inhibition on human liver cytochrome P450 3A4 by constituents of fennel (Foeniculum vulgare): identification and characterization of a mechanism-based inactivator. *J Agric Food Chem* 2007; 55: 10162–10167.
211. Ganzera M, Schneider P, Stuppner H. Inhibitory effects of the essential oil of chamomile (Matricaria recutita L.) and its major constituents on human cytochrome P450 enzymes. *Life Sci* 2006; 78: 856–861.
212. Nowack R, Nowak B. Herbal teas interfere with cyclosporin levels in renal transplant patients. Nephrol Dial Transplant. 2005;20:2554–6.
213. Qiu J-X, Zhou Z-W, He Z-X, et al. Estimation of the binding modes with important human cytochrome P450 enzymes, drug interaction potential, pharmacokinetics, and hepatotoxicity of ginger components using molecular docking, computational, and pharmacokinetic modeling studies. Drug Des Devel Ther. 2015;9:841–66.
214. Kim HJ, Kim IS, Rehman SU, et al. Effects of 6-paradol, an unsaturated ketone from gingers, on cytochrome P450-mediated

drug metabolism. *Bioorg Med Chem Lett*. Epub ahead of print 20 February 2017. https://doi.org/10.1016/j.bmcl.2017.02.047.
215. Shalansky S, Lynd L, Richardson K, et al. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. Pharmacotherapy. 2007;27:1237–47.
216. Yap KY-L, See CS, Chan A. Clinically-relevant chemotherapy interactions with complementary and alternative medicines in patients with cancer. *Recent Pat Food Nutr Agric* 2010; 2: 12–55.
217. Cho H-J, Yoon I-S. Pharmacokinetic Interactions of Herbs with Cytochrome P450 and P-Glycoprotein. *Evid Based Complement Alternat Med*; 2015. Epub ahead of print 2015. https://doi.org/10.1155/2015/736431.
218. Etheridge AS, Black SR, Patel PR, et al. An in vitro evaluation of cytochrome P450 inhibition and P-glycoprotein interaction with goldenseal, Ginkgo biloba, grape seed, milk thistle, and ginseng extracts and their constituents. Planta Med. 2007;73:731–41.
219. Mooiman KD, Maas-Bakker RF, Hendrikx JJMA, et al. The effect of complementary and alternative medicines on CYP3A4-mediated metabolism of three different substrates: 7-benzyloxy-4-trifluoromethyl-coumarin, midazolam and docetaxel. J Pharm Pharmacol. 2014;66:865–74.
220. Zou L, Harkey MR, Henderson GL. Effects of herbal components on cDNA-expressed cytochrome P450 enzyme catalytic activity. Life Sci. 2002;71:1579–89.
221. Shi S, Klotz U. Drug interactions with herbal medicines. Clin Pharmacokinet. 2012;51:77–104.
222. Deng Y, Bi H, Zhao L, et al. Induction of cytochrome P450 3A by the Ginkgo biloba extract and bilobalides in human and rat primary hepatocytes. Drug Metab Lett. 2008;2:60–6.
223. Scott GN, Elmer GW. Update on natural product–drug interactions. Am J Health Syst Pharm. 2002;59:339–47.
224. Unger M. Pharmacokinetic drug interactions involving Ginkgo biloba. Drug Metab Rev. 2013;45:353–85.
225. Naccarato M, Yoong D, Gough K. A potential drug-herbal interaction between Ginkgo biloba and efavirenz. J Int Assoc Physicians AIDS Care (Chic). 2012;11:98–100.
226. Wang R, Zhang H, Sun S, et al. Effect of Ginkgo Leaf Tablets on the Pharmacokinetics of Amlodipine in Rats. Eur J Drug Metab Pharmacokinet. 2016;41:825–33.
227. Hao M, Ba Q, Yin J, et al. Deglycosylated ginsenosides are more potent inducers of CYP1A1, CYP1A2 and CYP3A4 expression in HepG2 cells than glycosylated ginsenosides. Drug Metab Pharmacokinet. 2011;26:201–5.
228. Hao M, Zhao Y, Chen P, et al. Structure-activity relationship and substrate-dependent phenomena in effects of ginsenosides on activities of drug-metabolizing P450 enzymes. PLoS ONE. 2008;3:e2697.
229. Hwang S-W, Han H-S, Lim KY, et al. Drug interaction between complementary herbal medicines and gefitinib. J Thorac Oncol. 2008;3:942–3.
230. Pal D, Mitra AK. MDR- and CYP3A4-mediated drug-herbal interactions. Life Sci. 2006;78:2131–45.
231. Goey AKL, Mooiman KD, Beijnen JH, et al. Relevance of in vitro and clinical data for predicting CYP3A4-mediated herb–drug interactions in cancer patients. Cancer Treat Rev. 2013;39:773–83.
232. Bilgi N, Bell K, Ananthakrishnan AN, et al. Imatinib and Panax ginseng: a potential interaction resulting in liver toxicity. Ann Pharmacother. 2010;44:926–8.
233. Engdal S, Nilsen OG. In vitro inhibition of CYP3A4 by herbal remedies frequently used by cancer patients. Phytother Res. 2009;23:906–12.
234. Fritz H, Seely D, Kennedy DA, et al. Green tea and lung cancer: a systematic review. Integr Cancer Ther. 2013;12:7–24.
235. Chung J, Choi D, Choi J. Effects of oral epigallocatechin gallate on the oral pharmacokinetics of verapamil in rats. Biopharm Drug Dispos. 2009;30:90–3.
236. Johnson SS, Oyelola FT, Ari T, et al. In vitro inhibitory activities of the extract of Hibiscus sabdariffa L. (family Malvaceae) on selected cytochrome P450 isoforms. *Afr J Tradit Complement Altern Med* 2013; 10: 533–540.
237. Jacquin-Porretaz C, Nardin C, Blanc D, et al. Cutaneous Toxicity Induced by Hibiscus Tea in a Patient Treated with Erlotinib. J Thorac Oncol. 2017;12:e47–8.
238. Guo J, Nikolic D, Chadwick LR, et al. Identification of human hepatic cytochrome P450 enzymes involved in the metabolism of 8-prenylnaringenin and isoxanthohumol from hops (Humulus lupulus L.). *Drug Metab Dispos* 2006; 34: 1152–1159.
239. Huang Y, Zheng S, Zhu H, et al. Effects of aescin on cytochrome P450 enzymes in rats. J Ethnopharmacol. 2014;151:583–90.
240. Pandit S, Ponnusankar S, Bandyopadhyay A, et al. Exploring the possible metabolism mediated interaction of Glycyrrhiza glabra extract with CYP3A4 and CYP2D6. Phytother Res. 2011;25:1429–34.
241. Nabekura T, Yamaki T, Ueno K, et al. Inhibition of P-glycoprotein and multidrug resistance protein 1 by dietary phytochemicals. Cancer Chemother Pharmacol. 2008;62:867–73.
242. Kawaguchi-Suzuki M, Frye RF, Zhu H-J, et al. The effects of milk thistle (Silybum marianum) on human cytochrome P450 activity. Drug Metab Dispos. 2014;42:1611–6.
243. Doehmer J, Eisenbraun J. Assessment of extracts from mistletoe (Viscum album) for herb–drug interaction by inhibition and induction of cytochrome P450 activities. Phytother Res. 2012;26:11–7.
244. Agus HH, Tekin P, Bayav M, et al. Drug interaction potential of the seed extract of Urtica urens L. (dwarf nettle). *Phytother Res* 2009; 23: 1763–1770.
245. Yu EL, Sivagnanam M, Ellis L, et al. Acute hepatotoxicity after ingestion of Morinda citrifolia (Noni Berry) juice in a 14-year-old boy. J Pediatr Gastroenterol Nutr. 2011;52:222–4.
246. Carr M, Klotz J, Bergeron M. Coumadin resistance and the vitamin supplement 'Noni'. Am J Hematol. 2004;77:103.
247. Kang Y-C, Chen M-H, Lai S-L. Potentially Unsafe Herb–drug Interactions Between a Commercial Product of Noni Juice and Phenytoin- A Case Report. Acta Neurol Taiwan. 2015;24:43–6.
248. Dresser GK, Wacher V, Wong S, et al. Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo. Clin Pharmacol Ther. 2002;72:247–55.
249. Hidaka M, Nagata M, Kawano Y, et al. Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. Biosci Biotechnol Biochem. 2008;72:406–11.
250. Li Z, Dong X, Wang D, et al. Effect of oligosaccharide esters and polygalaxanthone Ill from Polygala tenuifolia willd towards cytochrome P450. Zhongguo Zhong Yao Za Zhi. 2014;39:4459–63.
251. Ryu CS, Oh SJ, Oh JM, et al. Inhibition of Cytochrome P450 by Propolis in Human Liver Microsomes. Toxicol Res. 2016;32:207–13.
252. Hanlon PR, Webber DM, Barnes DM. Aqueous extract from Spanish black radish (Raphanus sativus L. Var. niger) induces detoxification enzymes in the HepG2 human hepatoma cell line. *J Agric Food Chem* 2007; 55: 6439–6446.
253. Prasad GVR, Wong T, Meliton G, et al. Rhabdomyolysis due to red yeast rice (Monascus purpureus) in a renal transplant recipient. Transplantation. 2002;74:1200–1.
254. Chen C-H, Uang Y-S, Wang S-T, et al. Interaction between Red Yeast Rice and CYP450 Enzymes/P-Glycoprotein and Its Implication for the Clinical Pharmacokinetics of Lovastatin. Evid Based Complement Alternat Med. 2012;2012:127043.

255. Fung WT, Subramaniam G, Lee J, et al. Assessment of extracts from red yeast rice for herb–drug interaction by in vitro and in vivo assays. Sci Rep. 2012;2:298.
256. Tang J-C, Zhang J-N, Wu Y-T, et al. Effect of the water extract and ethanol extract from traditional Chinese medicines Angelica sinensis (Oliv.) Diels, Ligusticum chuanxiong Hort. and Rheum palmatum L. on rat liver cytochrome P450 activity. *Phytother Res* 2006; 20: 1046–1051.
257. Gao J, Shi Z, Zhu S, et al. Influences of processed rhubarbs on the activities of four CYP isozymes and the metabolism of saxagliptin in rats based on probe cocktail and pharmacokinetics approaches. J Ethnopharmacol. 2013;145:566–72.
258. Hellum BH, Nilsen OG. The in vitro inhibitory potential of trade herbal products on human CYP2D6-mediated metabolism and the influence of ethanol. Basic Clin Pharmacol Toxicol. 2007;101:350–8.
259. Schrøder-Aasen T, Molden G, Nilsen OG. In vitro inhibition of CYP3A4 by the multiherbal commercial product Sambucus Force and its main constituents Echinacea purpurea and Sambucus nigra. Phytother Res. 2012;26:1606–13.
260. Chen F, Li L, Tian D-D. Salvia miltiorrhiza Roots against Cardiovascular Disease: consideration of Herb–Drug Interactions. Biomed Res Int. 2017;2017:9868694.
261. Quaye O, Cramer P, Ofosuhene M, et al. Acute and Subchronic Toxicity Studies of Aqueous Extract of Desmodium adscendens (Sw) DC. J Evid Based Complementary Altern Med. 2017;22:753–9.
262. Herb–Drug Interactions: Starflower oil | Starflower | Medicinal Plants, http://medicinalplants.us/herb-drug-interactions-starflower-oil (accessed 16 June 2018).
263. Xie R, Tan LH, Polasek EC, et al. CYP3A and P-glycoprotein activity induction with St. John's Wort in healthy volunteers from 6 ethnic populations. *J Clin Pharmacol* 2005; 45: 352–356.
264. Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA. 2003;290:1500–4.
265. Xu H, Williams KM, Liauw WS, et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol. 2008;153:1579–86.
266. Barnes J, Anderson LA, Phillipson JD. St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties. *J Pharm Pharmacol* 2001; 53: 583–600.
267. Mouly S, Lloret-Linares C, Sellier P-O, et al. Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort? Pharmacol Res. 2017;118:82–92.
268. Schwarz UI, Hanso H, Oertel R, et al. Induction of intestinal P-glycoprotein by St John's wort reduces the oral bioavailability of talinolol. Clin Pharmacol Ther. 2007;81:669–78.
269. Hennessy M, Kelleher D, Spiers JP, et al. St John's Wort increases expression of P-glycoprotein: implications for drug interactions. Br J Clin Pharmacol. 2002;53:75–82.
270. Imai H, Kotegawa T, Tsutsumi K, et al. The recovery time-course of CYP3A after induction by St John's wort administration. Br J Clin Pharmacol. 2008;65:701–7.
271. Yang A-K, He S-M, Liu L, et al. Herbal interactions with anticancer drugs: mechanistic and clinical considerations. Curr Med Chem. 2010;17:1635–78.
272. Smith P, Bullock JM, Booker BM, et al. The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate. *Pharmacotherapy* 2004; 24: 1508–1514.
273. Borrelli F, Izzo AA. Herb–drug interactions with St John's wort (Hypericum perforatum): an update on clinical observations. AAPS J. 2009;11:710–27.
274. Brahmi Z, Niwa H, Yamasato M, et al. Effective cytochrome P450 (CYP) inhibitor isolated from thyme (Thymus saturoides) purchased from a Japanese market. Biosci Biotechnol Biochem. 2011;75:2237–9.
275. Aristatile B, Al-Assaf AH, Pugalendi KV. Carvacrol ameliorates the PPAR-A and cytochrome P450 expression on D-galactosamine induced hepatotoxicity rats. Afr J Tradit Complement Altern Med. 2014;11:118–23.
276. De-Oliveira AC, Ribeiro-Pinto LF, Otto SS, et al. Induction of liver monooxygenases by beta-myrcene. Toxicology. 1997;124:135–40.
277. Chang-Liao WL, Chien CF, Lin LC, et al. Isolation of gentiopicroside from Gentianae Radix and its pharmacokinetics on liver ischemia/reperfusion rats. J Ethnopharmacol. 2012;141:668–73.
278. García JJ, Fernández N, Diez MJ, et al. Influence of two dietary fibers in the oral bioavailability and other pharmacokinetic parameters of ethinyloestradiol. Contraception. 2000;62:253–7.
279. Bromley J, Hughes BGM, Leong DCS, et al. Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. Ann Pharmacother. 2005;39:1566–9.
280. Mbeunkui F, Grace MH, Lategan C, et al. In vitro antiplasmodial activity of indole alkaloids from the stem bark of Geissospermum vellosii. J Ethnopharmacol. 2012;139:471–7.
281. Samojlik I, Petković S, Stilinović N, et al. Pharmacokinetic Herb–Drug Interaction between Essential Oil of Aniseed (Pimpinella anisum L., Apiaceae) and Acetaminophen and Caffeine: A Potential Risk for Clinical Practice. *Phytother Res* 2016; 30: 253–259.
282. Samojlik I, Mijatović V, Petković S, et al. The influence of essential oil of aniseed (Pimpinella anisum, L.) on drug effects on the central nervous system. *Fitoterapia* 2012; 83: 1466–1473.
283. Juanbeltz Zurbano R, Pérez-Fernández MD, Tirapu Nicolás B, et al. Complementary medicine use in cancer patients receiving intravenous antineoplastic treatment. Farm Hosp. 2017;41:589–600.
284. McLay JS, Stewart D, George J, et al. Complementary and alternative medicines use by Scottish women with breast cancer. What, why and the potential for drug interactions? *Eur J Clin Pharmacol* 2012; 68: 811–819.
285. Kremser T, Evans A, Moore A, et al. Use of complementary therapies by Australian women with breast cancer. Breast. 2008;17:387–94.
286. Morris KT, Johnson N, Homer L, et al. A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. Am J Surg. 2000;179:407–11.
287. Molassiotis A, Scott JA, Kearney N, et al. Complementary and alternative medicine use in breast cancer patients in Europe. Support Care Cancer. 2006;14:260–7.
288. Boon H, Stewart M, Kennard MA, et al. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. J Clin Oncol. 2000;18:2515–21.
289. Amini A, Masoumi-Moghaddam S, Ehteda A, et al. Bromelain and N-acetylcysteine inhibit proliferation and survival of gastrointestinal cancer cells in vitro: significance of combination therapy. J Exp Clin Cancer Res. 2014;33:92.
290. Amini A, Masoumi-Moghaddam S, Ehteda A, et al. Potentiation of chemotherapeutics by bromelain and N-acetylcysteine: sequential and combination therapy of gastrointestinal cancer cells. Am J Cancer Res. 2016;6:350–69.
291. Hsu C-H, Cheng A-L. Clinical studies with curcumin. Adv Exp Med Biol. 2007;595:471–80.
292. Vallianou NG, Evangelopoulos A, Schizas N, et al. Potential anticancer properties and mechanisms of action of curcumin. Anticancer Res. 2015;35:645–51.
293. Wilson KS. Regression of follicular lymphoma with Devil's Claw: coincidence or causation? Curr Oncol. 2009;16:67–70.

294. Chang H-K, Shin M-S, Yang H-Y, et al. Amygdalin induces apoptosis through regulation of Bax and Bcl-2 expressions in human DU145 and LNCaP prostate cancer cells. Biol Pharm Bull. 2006;29:1597–602.
295. Khacha-Ananda S, Tragoolpua K, Chantawannakul P, et al. Propolis extracts from the northern region of Thailand suppress cancer cell growth through induction of apoptosis pathways. Invest New Drugs. 2016;34:707–22.
296. Elnakady YA, Rushdi AI, Franke R, et al. Characteristics, chemical compositions and biological activities of propolis from Al-Bahah. Saudi Arabia. Sci Rep. 2017;7:41453.
297. Ren K, Zhang W, Wu G, et al. Synergistic anti-cancer effects of galangin and berberine through apoptosis induction and proliferation inhibition in oesophageal carcinoma cells. Biomed Pharmacother. 2016;84:1748–59.
298. Rouhollahi E, Zorofchian Moghadamtousi S, Paydar M, et al. Inhibitory effect of Curcuma purpurascens BI: Rhizome on HT-29 colon cancer cells through mitochondrial-dependent apoptosis pathway. BMC Complement Altern Med 2015; 15: 15.
299. Cassileth BR, Lucarelli CD. Herb–drug Interactions in Oncology. PMPH-USA, 2003.
300. Zeller T, Muenstedt K, Stoll C, et al. Potential interactions of complementary and alternative medicine with cancer therapy in outpatients with gynecological cancer in a comprehensive cancer center. J Cancer Res Clin Oncol. 2013;139:357–65.
301. Cheng C-W, Fan W, Ko S-G, et al. Evidence-based management of herb–drug interaction in cancer chemotherapy. Explore (NY). 2010;6:324–9.
302. Brantley SJ, Graf TN, Oberlies NH, et al. A systematic approach to evaluate herb–drug interaction mechanisms: investigation of milk thistle extracts and eight isolated constituents as CYP3A inhibitors. Drug Metab Dispos. 2013;41:1662–70.
303. Butterweck V, Derendorf H, Gaus W, et al. Pharmacokinetic herb–drug interactions: are preventive screenings necessary and appropriate? Planta Med. 2004;70:784–91.
304. Raucy JL. Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. Drug Metab Dispos. 2003;31:533–9.
305. Harkey MR, Henderson GL, Gershwin ME, et al. Variability in commercial ginseng products: an analysis of 25 preparations. Am J Clin Nutr. 2001;73:1101–6.
306. Tsai H-H, Lin H-W, Simon Pickard A, et al. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. Int J Clin Pract. 2012;66:1056–78.
307. Tadic D, Spasojevic IB, Tomasevic ZI, et al. Oral administration of antineoplastic agents: the challenges for healthcare professionals. J BUON. 2015;20:690–8.
308. Yap KYL, Kuo EY, Lee JJJ, et al. An onco-informatics database for anticancer drug interactions with complementary and alternative medicines used in cancer treatment and supportive care: an overview of the OncoRx project. Support Care Cancer. 2010;18:883–91.
309. Memorial Sloan Kettering Cancer Center, https://www.mskcc.org/. Accessed 27 March 2018.