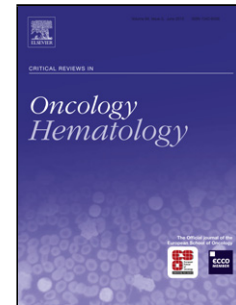


Journal Pre-proof

Potential Cytochrome P450-mediated pharmacokinetic interactions between herbs, food, and dietary supplements and cancer treatments

Paul Gougis, Marc Hilmi, Arthur Geraud, Olivier Mir, Christian Funck-Brentano



PII: S1040-8428(21)00130-X
DOI: <https://doi.org/10.1016/j.critrevonc.2021.103342>
Reference: ONCH 103342

To appear in: *Critical Reviews in Oncology / Hematology*

Received Date: 30 November 2020
Revised Date: 6 April 2021
Accepted Date: 25 April 2021

Please cite this article as: { doi: <https://doi.org/>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

Potential Cytochrome P450-mediated pharmacokinetic interactions between herbs, food, and dietary supplements and cancer treatments.

Paul Gougis¹⁻², MD, Marc Hilmi¹, MSc, MD, Arthur Geraud^{1,3}, MD, Olivier Mir⁴, MD, Ph.D., Christian Funck-Brentano¹, MD, Ph.D.

¹: Sorbonne Université, INSERM CIC Paris-Est, AP-HP, ICAN, Pitié-Salpêtrière Hospital, Department of Pharmacology, F-75013 Paris, France;

²: CLIP² Galilée, Department of Medical Oncology Pitié-Salpêtrière Hospital, F-75013 Paris, France;

³: Early Drug Development Department (DITEP), Gustave Roussy, Villejuif, France;

⁴: Department of Ambulatory Care, Gustave Roussy Cancer Campus, Villejuif, France.

Corresponding author:

Paul Gougis, Centre d'Investigation Clinique (CIC), Hôpital Pitié-Salpêtrière
47-83 Blvd de l'Hôpital, 75013 Paris, France

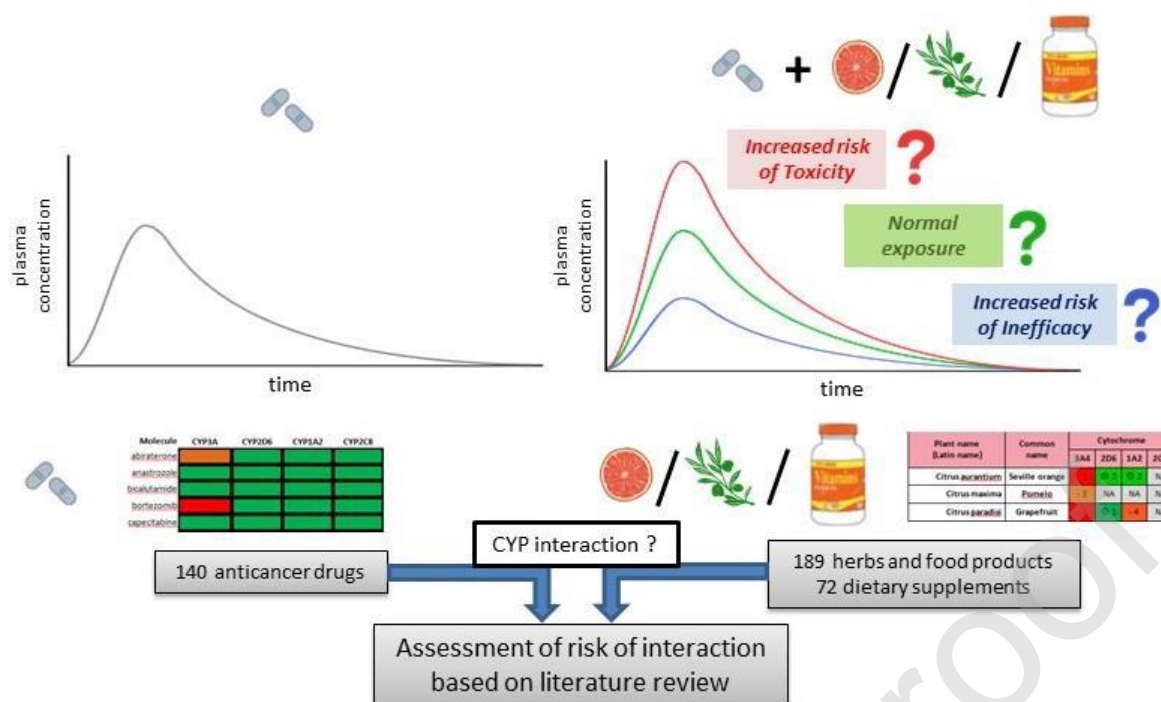
Phone: +33 (0) 1 42 17 85 31

Fax: + 33 (0) 1 42 17 85 32

E-mail: paul.gougis@aphp.fr

Words: Abstract: 220 (max 350), text: 3062 (max 5000), Figures & Tables: 5 tables

Graphical abstract



Highlights

- Herbs food and dietary supplements (HFDS) could modify cytochromes' activity
- Most anticancer drugs are metabolized by cytochromes
- Pharmacokinetic interactions via cytochromes could be predicted
- An easy-to-read table has been generated to cross and anticipate HFDS-drug interactions

Abstract:

Herbs, food and dietary supplements (HFDS), can interact significantly with anticancer drug treatments via cytochrome p450 isoforms (CYP) CYP3A4, CYP2D6, CYP1A2, and CYP2C8. The objective of this review was to assess the influence of HFDS compounds on these cytochromes.

Interactions with CYP activities were searched for 189 herbs and food products, 72 dietary supplements in Web of Knowledge® databases. Analyses were made from 140 of 3,125 clinical trials and 236 of 3,374 *in vitro*, animal model studies or case reports.

18 trials were found to report direct interactions between 9 HFDS with 8 anticancer drugs. 21 HFDS were found to interact with CYP3A4, a major metabolic pathway for many anticancer drugs. All 261

HFDS were classified for their interaction with the main cytochromes P450 involved in the metabolism of anticancer drugs.

We provided an easy-to-use colour-coded table to easily match potential interactions between 261 HFDS and 117 anticancer drugs.

Abbreviations:

ABC: ATP-binding cassette; AM: animal model; CAM: complementary and alternative medicine; CYP: cytochromes; EGCG: epigallocatechin gallate; FDA: food and drug administration; GFJ: grapefruit juice; HFDI: herb or food-drug interaction; HFDS: herb food and dietary supplements; IC50: half-maximal inhibitory concentration; ind: inducer; inh: inhibitor; iVit: *in vitro*; NA: not available; NCS: not clinically significant; NS: not significant; PD: pharmacodynamics; PK: pharmacokinetics; PKI: protein kinase inhibitors; PXR: pregnane X receptor; TS is the field tag standing for “Topics” in the “Web of Knowledge” research engine.

Keywords

Herb-drug interaction; food-drug interaction; anticancer drugs; oncology; dietary supplements; cytochromes; pharmacokinetics

1. Introduction

The use of complementary and alternative medicine (CAM) has considerably increased in Western countries and is fundamental in many health-care systems [1]. In Africa, phytotherapy is used by 80% of the population [2]. The prevalence of herbal medicine use in the healthy US population was 12% in 1997 and has increased to one third in 2015 [1]. In this study [1], cancer was the second most frequent pathology associated with the use of herbal medicine (43%). Dy *et al.* reported that in patients accrued in a phase 1 clinical trials for the treatment of their cancer, 88% of patients used CAM at least once, and 93% of them used herbs, food and dietary supplements (HFDS) [3].

Several herb-drug interactions or food-drug interactions (HFDI) have been extensively described, such as the induction of cytochrome P-450 3A4 (CYP3A4) by Saint-John's wort, or the inhibition of

CYP3A4 by grapefruit juice (GFJ). Other phytotherapies are often considered harmless, although there is growing evidence that their use can lead to HFDI with severe or fatal outcomes, transplant rejection, cardiovascular collapses among others [4]. Bush *et al.* [5] prospectively investigated potential herb-drug interactions in unselected patients in 6 clinics. They found that 122 of 804 patients (15%) were using herbal medicine, of whom 49 (40%) had a potential herb-drug interaction and 8 had interactions with clinical consequences (7% of herbal medicine users).

Engdal and colleagues [6] did similar research among 42 cancer patients using herbal remedies and receiving anticancer drugs. Based on a literature search in medical databases, they found 47 PK interactions involving CYP enzymes and p-glycoprotein transporters. Most oncology treatments have a narrow therapeutic index, and small pharmacokinetic (PK) modifications may have dramatic consequences on treatment efficacy or safety [7].

In vitro and clinical drug interaction studies have become essential for the approval of drugs by regulatory agencies [8–10]. Drug-drug interactions, involving CYP3A4 for example, can be anticipated using ketoconazole (CYP 3A4 inhibitor) or rifampicin (CYP3A inducer) in clinical studies, and measuring the modification of drug exposure before and after the inducer/inhibitor. However, inhibition or induction of other CYPs has been studied less.

In a preliminary search, we identified the main cytochromes (CYP) involved in the biotransformation of anticancer drugs. We then summarised clinical, *in vivo* and *in vitro* data, with a 2-step systematic search of herb drugs, dietary supplements and food interactions on cytochromes. A reproducible algorithm was used to assess the level of evidence of the potential for interactions.

The main objective of the study was to assess interactions between HFDS and cytochromes P450 CYP3A4, CYP2D6, CYP1A2, and CYP2C8 which are the main clinically relevant cytochromes involved in anticancer drugs metabolism. The secondary objective of the study was to find case reports, *in vitro* or animal model data on the interaction of HFDS with the same cytochromes.

2. Material and methods

2.1. Preliminary search for anticancer drugs

A preliminary search was needed to identify the main cytochromes involved in the metabolism of anticancer drugs. We used regulatory sources from the last updated food and drug administration (FDA) labels of each anticancer drug [11]. Dailymed website [12] and IBM Micromedex® [13] were also used. When no or few data were available, an additional search was done through MEDLINE®. Interactions could have been proven clinically or *in vitro*. Interactions with cytochromes were classified as follows:

- Known- if there was clinically significant evidence that the drug is a substrate of the cytochrome
- Possible - if there was only *in vitro* or preclinical evidence, or if the interaction of the CYP inhibitor/inducer was significant but minor (<20% of AUC change)
- No interaction - if there was no evidence of interaction

2.2 Main search strategy

The search was done in two steps. First, clinical studies were searched for interactions with relevant cytochromes involved in anticancer drug metabolism found in the preliminary search. When no data was found, a second search was made to retrieve *in vitro* assays, animal studies, or case reports.

This search was independently done for each HFDS using Web of Science® databases, which include MEDLINE® database, from 1966 to November 2018, with no language limitation and using the following search terms:

- #1 TS = (CYP3A4 OR CYP3A OR CYP1A2 OR CYP2D6 OR CYP2C8) NOT TS= review
- #2 TS = (clinical OR volunteers OR subjects OR patients)
- #3 TS = (case OR reports OR rat OR rabbit OR mouse OR dog OR animal OR "in vivo" OR "in vitro" OR assay OR microsome OR preclinical)

#4 TS = (“common name” OR “Latin name” OR “main active compound”)

#5 #1 AND #2 AND #4

#6 #1 AND #3 AND #4

Common names and Latin names were used in the search line #4. For example, for green tea, for which the Latin name is *Camelia Sinensis*, line #4 was:

#4 TS = (“green tea” OR “camellia sinensis”)

All search lines are available in Supplementary Table 1. When appropriate, the main active compound was added. When the common name was a part of the Latin name (*i.e.*, “*aloe vera*” and *aloe*), the search was simplified to the common name. Search line #5 was used for clinical trial results. When no data was found with search line #5, search line #6 was used to search for animal models, *in vitro* assays, and case reports.

The list of HFDS was created from the web site “about herbs” [14] and completed with HFDS widely used in Europe and the US.

2.3. Selection criteria

2.3.1. Inclusion criteria for clinical trials:

- 1 – HFDS was administered alone (no concomitant HFDS or phytotherapy mixture or any other drug)
- 2 – The clinical trial had a control group (cross-over or parallel)
- 3 – The main objective of the trial was to assess the interaction of an HFDS with a drug
- 4 – The drug was a known probe of the CYP (e.g., midazolam for CYP3A4), or the interaction was only explained by an interaction with the concerned CYP.

2.3.2. Inclusion criteria for case reports:

- 1 – No other HFDS could explain the interaction

2 – Imputability score, as defined by the French Imputability method, was either plausible (I2), likely (I3), or very likely (I4) [15].

2.3.3. Inclusion criteria for animal models:

- 1 – HFDS was administered alone (no concomitant HFDS or phytotherapy mixture or any other drug)
- 2 – The assay had a control group (cross-over or parallel)
- 3 – The assay used rat, mouse, rabbit, dog, pig or monkey

2.3.4. Inclusion criteria for *in vitro* assays:

- 1 – HFDS was tested alone (no HFDS mixtures)
- 2- The assay was controlled using references (ketoconazole for CYP3A4 inhibition for example), or a half-maximal inhibitory concentration (IC₅₀) was measured
- 3 – The assay used microsomes (human or animal) or quantified the expression of cytochromes by reverse transcriptase-polymerase chain reaction on cell lines or assessed binding to pregnane X receptor (PXR)

2.4. Classification of the level of evidence

We first identified direct inhibitions between HFDS and oncolytic substrates. Secondly, interactions of HFDS with human cytochromes were assessed using a scale for the level of evidence. A scale from 1 (highest level of evidence) to 5 (lowest level of evidence) was established empirically to assess the level of evidence of each HFDS with each cytochrome (Table 1). When several clinical trials were found to confirm the interaction, the level of evidence was 1. When few *in vitro* data were found, the level of evidence was 5.

The scale is made of 5 levels. Grade 1 and 2 are clinically relevant levels, and grade 4 and 5 are based on preclinical data of uncertain clinical relevance. Because interactions which are clinically mild but significant, with a modification of AUC <20%, are barely relevant, we combined them to a high level of *in vitro* and animal models data proof, which also has an uncertain clinical pertinence.

Table 1: Level of evidence: for interaction between an HFDS and a cytochrome

“⊖” is used when no interaction with the cytochrome is found, “-” for cytochrome inhibition, “+” for cytochrome induction, “+/-” when both inhibition and induction data are found, and NA when no data is available

Unknown	NA	No available data
No interaction	⊖ 1	At least 2 controlled clinical trials and none of them with an interaction
	⊖ 2	1 clinical result found which had no interaction
	⊖ 3	At least 2 different types of preclinical assays (animal model & <i>in vitro</i>) and none of them with an interaction
	⊖ 4	At least 3 <i>in vitro</i> assays or animal model with no significant interactions, more than 67% of the assays with no significant interaction and all 3 assays with full extracts
	⊖ 5	2 or less <i>in vitro</i> assays available only, and none of them with an interaction
CYP inhibition	- 1	At least 2 controlled clinical trials with proved CYP inhibition
	- 2	At least 1 clinical result with proved CYP inhibition with AUC modification >20%
	- 3	At least 1 clinical result with mild but significant (AUC of the probe increased by less than 20%) CYP inhibition, or 1 clinical result with a major compound of the plant, or 1 clinical trial with the result that could be explained by other CYP interaction or transporter (p-gp)
	- 4	At least 2 different types of preclinical studies or well-documented case reports that documented the inhibition, or 3 <i>in vitro</i> assays or animal models only but all assays with significant interactions. If both induction and inhibition were present, more than 67% induction was required
	- 5	Only <i>in vitro</i> data available, or inhibition with one of the main compounds
CYP induction	+ 1	At least 2 controlled clinical trials with proved CYP induction
	+ 2	At least 1 clinical result with proved CYP induction with AUC modification >20%
	+ 3	At least 1 clinical result with mild but significant (AUC of the probe decreased by less than 20%) CYP induction, or 1 clinical result with a major compound of the plant
	+ 4	At least 2 different types of preclinical studies or well-documented case reports that documented the induction, or 3 <i>in vitro</i> assays or animal models only but all assays with significant interactions. If both induction and inhibition were present, more than 67% induction was required
	+ 5	Only <i>in vitro</i> data available to document induction or induction with one of the main compounds
Conflicting data	+/- C	Conflicting clinical data with both inhibition and induction
	+/- p	Conflicting preclinical data with both inhibition and induction

AUC: area under curve; CYP: cytochromes; p-gp: p-glycoprotein; NA: no data available

3. Results

3.1. Direct interactions

Direct clinical interactions between HFDS and anticancer drugs were retrieved from the first step of the main search. We found 18 trials and reports with 9 different HFDS and 8 anticancer drugs. The results are summarised in Table 2.

Table 2: Direct pharmacokinetic interactions between HFDS and anticancer drugs

HFDS	anticancer drug	number of patient	conclusion	Reference
cannabis	irinotecan	17	no significant modification of AUC for irinotecan and its active metabolite SN-38	[16]
	docetaxel	14	no significant modification of AUC	
curcumin alone	tamoxifen	16	trend for endoxifen AUC decrease (-7.7%; p = 0.07)	[17]
curcumin + piperin	tamoxifen	16	AUC of endoxifen decreased by 12.4%	[17]
	everolimus	1 (x2)	C _{through} decreased between 2 and 3 folds	[18]
echinacea	docetaxel	10	no significant modification for AUC	[19]
garlic	docetaxel	10	no significant modification for AUC	[20]
grapefruit	docetaxel	1	AUC increased by 2.6 fold	[21]
	oral etoposide	6	AUC decreased by 26%	[22]
	ibrutinib	8	AUC of ibrutinib increased by 2.1 fold	[23]
	sunitinib	8	AUC increased by 11%	[24]
	imatinib	4	no significant modification for C _{max} and C _{through}	[25]
milk thistle	irinotecan	6	no significant modification of AUC for irinotecan and its active metabolite SN38	[26]
Saint John's wort	irinotecan	5	AUC of the active metabolite SN-38 decreased by 42%	[27]
	docetaxel	10	AUC decreased by 11%	[28]
	imatinib	10	AUC decreased by 32%	[29]
	imatinib	12	AUC decreased by 30%	[30]
soy	tamoxifen	136 vs. 154 controls	no significant modification of AUC for tamoxifen and its active metabolite endoxifen	[31]



























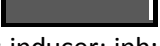
AUC: area under curve

3.2. Preliminary search results

Anti-cancer drugs approved by the FDA or the European Medicine Agency (EMA) were studied (Supplementary Table 2). Table 3 summarises the most prescribed treatments.

CYP1A2 metabolises bendamustine, carmustine, and erlotinib. Lapatinib was the only drug for which CYP2C19 appears to have a role. CYP2C8 metabolised 5.9% of the treatments, including paclitaxel. CYP2C9 plays a role in the metabolism of imatinib, cabozantinib, ruxolitinib.

Table 3: Influence of inhibition or induction of CYP on main drugs used in oncology (full Table available as supplementary data, Table 1)

Molecule	CYP3A inh ind	CYP2D6	CYP1A2	CYP2C8	Reference
abiraterone					[11–13]
anastrozole					[11–13]
bicalutamide					[11–13]
bortezomib					[11]
capecitabine					[11–13]
cabozantinib					[11,32]
carboplatin					[11–13]
cisplatin					[11–13]
cobimetinib					[11–13]
crizotinib					[11–13]
cyclophosphamide					[33,34]
cytarabine					[35]
dabrafenib					[11–13]
dasatinib					[36]
daunorubicine					[11–13]
docetaxel					[11,37]
doxorubicin					[11–13,38]
enzalutamide					[11–13]
epirubicin					[11–13]
eribulin					[11–13]
erlotinib					[11,39]
etoposide					[40]
everolimus					[11–13]
exemestane					[11–13]
fluorouracil					[11–13]
fulvestrant					[11–13]
gemcitabine					[11–13]
ibrutinib					[11–13]
ifosfamide					[11–13]
imatinib					[11–13]

cytochromes; DCI: ind: inducer; inh: inhibitor; GnRH: gonadotropin-releasing hormone.

CYP:

irinotecan					[11–13]
lenalidomide					[11–13]
letrozole					[11–13]
melphalan					[11–13]
methotrexate					[11–13]
nilotinib					[11–13]
osimertinib					[11–13,41]
oxaliplatin					[11–13]
paclitaxel					[11–13]
palbociclib					[11–13]
pazopanib					[32,36]
pemetrexed					[11–13]
ruxolitinib					[11–13]
sorafenib					[11,32]
sunitinib					[32,36]
tamoxifen					[42,43]
thalidomide					[11–13]
trametinib					[11–13]
vemurafenib					[11–13]
vincristine					[11–13]
immunoglobulin					[44]
GnRH analogues					[45,46]

Colour code:

- **White:** no influence of cytochrome induction or inhibition.
- **Light grey:** preclinical data only showing that the drug is a substrate for this cytochrome
- **Dark grey:** clinical data available (concomitant use of ketoconazole modifies drug's AUC for CYP3A4 inhibition for example)

3.3. HFDS interaction with cytochromes

The literature search identified 3135 hits for clinical trials and 3374 hits for the 261 HFDS. Five abstracts of congresses were not available. 140 clinical trials and 236 *in vitro*, animal model studies or case reports were found (169 *in vitro*, 65 animal model, 2 case reports). Table 4 summarises the results of the research for each HFDS and each cytochrome of the 34 most prescribed HFDS in Europe and the US. Full results (261 HFDS) are presented in Table 5, according to the colour code available in Table 1.

Table 4: Induction or inhibition of 34 most used phytotherapies in Europe and in the US on the expression of CYP. The colour code is available in Table 1.

Plant name (Latin name)	Common name	3A4	2D6	1A2	2C8
<i>Cimicifuga racemosa</i>	Black cohosh	Clin: NCS x2[47,48]	Clin: Mild inh x1[47] NCS x1[49]	Clin: NCS x1[47]	iVit : NS x2 [50,51]
<i>Allium sativum</i>	Garlic	Clin: NCS x5[20,52–56]	Clin: NCS x3[52–54]	Clin: NCS x2[53,54]	iVit : NS x1[50]
<i>Camellia sinensis</i>	Green tea*	Clin: NCS x1[57] inh x1[58]	Clin: NCS x2[57,58]	Clin: NCS x2[58]	iVit : inh x1[59]
<i>Citrus paradisi</i>	Grapefruit**	Clin: Inh x24[60–78,24,79,23,80–84] NCS: x1[25]	Clin: NCS x2[70,78]	Clin: inh x1[85] NCS x3[86–88]	NA
<i>Crataegus monogyna</i>	Hawthorn	iVit: ind x1[89] inh x1[90]	iVit : inh x1[90]	iVit : inh x1[90]	NA
<i>Curcuma longa</i>	Tumeric***	Clin ⁺ : NCS x3[91–93]	Clin: inh x1[92]	Clin: inh x1[94]	iVit : NS (curcumenol)[95]
<i>Desmodium adsendens</i>	Desmodium	NA	NA	NA	NA
<i>Echinacea purpurea</i>	Echinacea	Clin: ind x2[96,97] NCS x2[19,98]	Clin : NCS x3 [49,97,98]	Clin: inh x1[97] NCS x1[98]	iVit : NS x2 [50,99]
<i>Garcinia mangostana</i>	Mangosteen	iVit: inh x4 [100–103]	iVit: inh x2 [102,103] NS x1[101]	iVit: inh x3 [100,102,103] NS x1[101]	iVit : inh x1[101]
<i>Ginkgo Biloba</i>	Ginkgo	Clin : NCS x5[53,54,104–106] ind x1[107] mild ind x1[108] inh x1[109]	Clin: NCS x5 [53,54,104,105,108]	Clin: NCS x4 [53,54,104,105]	iVit: inh x3 [99,110,111]
<i>Glycine max</i>	Soy	Clin : NCS x2 [112,113] ind genistein[114]	Clin: NCS x1[31]	Clin: inh genistein[115] / daidzein[116]	iVit: inh x1[117]
<i>Hedera helix</i>	English ivy	iVit : NS x1[118]	iVit: inh x1[118]	iVit : NS x1[118]	iVit: inh x1[118]
<i>Hydrastis canadensis</i>	Goldenseal	Clin: inh x3 [47,119,120] NCS x1[121]	Clin: Inh x2 [47,49]	Clin: NCS x1[47]	iVit: inh x1[110] NS x1[51]
<i>Hypericum perforatum</i>	Saint John's wort	Clin: ind x12 [29,30,53,54,122–133] NCS x2 [134,135]	Clin: NCS x5 [49,53,54,127,134]	Clin: NCS x3 [53,54,136]	Clin: ind x1[137]
<i>Lepidium meyenii</i>	Maca	NA	NA	NA	NA
<i>Linum usitatissimum</i>	Flaxseed	NA	NA	NA	NA
<i>Lycium barbarum</i>	Goji	iVit: inh x2[103,138] ind x1[139]	iVit: inh x1[138]	iVit: inh x1[103]	NA
<i>Matricaria recutita</i>	Chamomile (German)	AM: NS x1[140] CR: inh x1[141] iVit: inh x2[142,143]	AM: NS x1[140] iVit: inh x1[142]	AM: inh x1[140] iVit: inh x1[142]	NA

Plant name (Latin name)	Common name	3A4	2D6	1A2	2C8
<i>Marrubium vulgare</i>	Horehound (white)	NA	NA	NA	NA
<i>Mentha piperita</i>	Peppermint	Clin: inh x1[144] NCS menthol[145]	AM: NS x1[140] iVit: inh x1[146]	Clin: NCS x1[147] menthol NCS x1[148]	NA
<i>Morinda citrifolia</i>	Noni	AM: inh x1[149] iVit: inh x2[6,103]	NA	iVit: inh[103]	NA
<i>Panax ginseng</i>	Ginseng (asian)	Clin: ind x1[150] NCS x5 [53,54,105,112,151]	Clin: Mild inh x1[53] NCS x2[54,151]	Clin: NCS x3 [53,54,151]	iVit: NS x1[110] AM: NS x1[152]
<i>Pausinystalia johimbe</i>	Yohimbe	NA	iVit: inh x1[153]	NA	NA
<i>Pelargonium sidoides</i>	Umckaloabo	NA	NA	NA	NA
<i>Piper methysticum</i>	Kava kava	Clin: NCS x2[47,119]	Clin: NCS x2[47,49]	Clin: NCS x1[47]	NA
<i>Prunus africana</i>	Pygeum	NA	NA	NA	NA
<i>Serenoa repens</i>	Saw palmetto	Clin: NCS x2[98,154]	Clin: NCS x2[98,154]	Clin: NCS x1[98]	iVit : inh x1[50] NS x1[51]
<i>Silybum marianum</i>	Milk thistle	Clin: NCS x5 [26,48,98,155,156]	Clin: NCS x3 [49,98,155]	Clin: NCS x2 [98,155]	iVit: NS x3 [51,157,158] inh x1[110]
<i>Stevia rebaudiana</i>	Stevia	iVit: inh&ind (steviol)[159]	iVit: NS (steviol)[159]	iVit: ind (steviol)[159]	NA
<i>Tanacetum parthenium</i>	Feverfew	iVit: inh x2[146,160]	iVit: inh x1[146]	iVit: inh x1[146]	NA
<i>Vaccinium macrocarpon</i>	Cranberry	Clin: inh x1[161] NCS x2[162,163]	iVit: NS x1[164]	Clin: NCS x1[163]	iVit : inh x1[50]
<i>Valeriana officinalis</i>	Valerian	Clin: NCS x2[47,165]	Clin: NCS x2[47,165]	Clin: NCS x1[47]	iVit : NS x2[50,51]
<i>Vitis vinifera</i>	Grape / wine	AM : inh x2[166,167] iVit: inh x6 [110,168–172] NS x2[173,174]	Clin: NCS x1[175]	Clin: ind x1[176]	iVit: NS x1[110]
<i>Zingiber officinale</i>	Ginger	AM: [177,178] ^o iVit: inh x6[179–184] ind x1[185] NS x5[164,186–189]	iVit: NS x8 [164,180,183,186–190]	iVit: inh x1[188] ind x1[185] NS x4 [164,186,187,189]	iVit: inh x2[187,191]

AM: animal model; Clin: clinical trials; CR: case reports; ind: cytochrome induction; inh: cytochrome inhibition; iVit: *in vitro*; NCS: no clinically significant interaction; NS: no significant preclinical interaction;

* Sunitinib: reduced bioavailability in animal model, not CYP mediated[192]

5-FU increased exposition in animal model[193]

Cyclophosphamide increased exposition in animal model[194]

Bortezomib(not carfilzomib) and ixazomib: boronic acid-based proteasome inhibitors, *in vitro* and animal model [195]

** Oral etoposide: decreased bioavailability in animal model [22]

*** Oral etoposide: increased bioavailability in animal model [196]

* Al-Jenoobi [92] described an increase of the DEX/3-MM ratio of 50% (CYP3A4 induction) with curcuma longa associated with piperine not considered significant due to small population p=0.12 NS

° Cyclosporin and tacrolimus: decreased bioavailability, probably not CYP mediated (increased gastric emptying)

Journal Pre-proof

Table 5: CYP interactions of 261 herb, food and dietary supplements

HFDS interactions, according to Table 1 level of evidence scale. HFDS with clinically proven interaction with CYP3A4 found in table 3 is in bold. “⊖” is used when no interaction with the cytochrome is found, “-” for cytochrome inhibition, “+” for cytochrome induction, “+/-” when both inhibition and induction data are found, and NA when no data is available. HFDS with a strong or moderate inhibitors or inducers effect on cytochromes according to FDA guidelines for drug-drug interactions [197] were blackboxed. Other interactions were mild.

Phytotherapy

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Acmella oleracea</i>	Spilanthes	NA	NA	NA	NA
<i>Aesculus hippocastanum</i>	Horse chestnut	- 4	- 5	+/- p	NA
<i>Agaricus subrufescens</i>	Agaricus	- 5	NA	NA	NA
<i>Aloe Vera</i>	Aloe	- 4	- 5	NA	NA
<i>Allium sativum</i>	Garlic	⊖ 1	⊖ 1	⊖ 1	⊖ 5
<i>Andrographis paniculata</i>	Andrographis	- 5	⊖ 5	- 5	NA
<i>Angelica sinensis</i>	Dong quai	+ 5	+ 5	+/- p	NA
<i>Annona muricata</i>	Soursop	- 5	- 5	⊖ 5	NA
<i>Arctium lappa</i>	Burdock	- 5	NA	NA	NA
<i>Arnica montana</i>	Arnica	NA	NA	NA	NA
<i>Artemisia annua</i>	Sweet wormwood	- 5	NA	NA	NA
<i>Arthrospira platensis</i>	Spirulina	⊖ 5	NA	- 5	NA
<i>Asimina triloba</i>	Pawpaw	NA	NA	NA	NA
<i>Aspalathus linearis</i>	Rooibos	- 5	NA	NA	- 5
<i>Asparagus cochinchinensis</i>	Tian men dong	NA	NA	NA	NA
<i>Astragalus membranaceus</i>	Astragalus	+/- p	⊖ 5	- 5	NA
<i>Averrhoa carambola</i>	Star fruit (Carambola)	- 4	NA	NA	NA
<i>Azadirachta indica</i>	Neem	NA	NA	NA	NA
<i>Borago officinalis</i>	Borage	NA	NA	NA	NA
<i>Boswellia serrata</i>	Indian olibanum	NA	NA	NA	NA
<i>Brassica oleracea</i>	Broccoli sprouts extracts / kale	- 3	- 5	- 5	NA
<i>Bupleurum falcatum (chinense)</i>	Thoroughwax	+/- p	+ 5	⊖ 3	NA
<i>Calendula officinalis</i>	Calendula	NA	NA	NA	NA
<i>Camellia sinensis</i>	Green tea	- 3	⊖ 1	⊖ 2	- 5
<i>Cannabis sativa</i>	Cannabis	⊖ 2	NA	- 4	NA
<i>Carica papaya</i>	Papaya	⊖ 5	NA	⊖ 5	NA
<i>Cassia angustifolia</i>	Senna (Alexandrina)	NA	NA	NA	NA

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Centella asiatica</i>	Gotu kola	- 5	- 5	⊖ 4	NA
<i>Cimicifuga racemosa</i>	Black cohosh	⊖ 1	- 3	⊖ 2	⊖ 5
<i>Citrus aurantifolia</i>	Lime	- 3	NA	NA	NA
<i>Citrus aurantium</i>	Seville orange	- 1	⊖ 2	⊖ 2	NA
<i>Citrus maxima</i>	Pomelo	- 3	NA	NA	NA
<i>Citrus paradisi</i>	Grapefruit	- 1	⊖ 1	- 4	NA
<i>Chamaemelum nobile</i>	Camomile (roman chamomile)	⊖ 5	⊖ 5	- 5	NA
<i>Chrysanthemum indicum</i>	Indian Chrysanthemum	⊖ 5	NA	NA	NA
<i>Chrysanthemum morifolium</i>	Chrysanthemum	⊖ 5	NA	NA	NA
<i>Cinnamomum verum/cassia</i>	Cinnamon	- 5	NA	NA	NA
<i>Cinnamomum camphora</i>	Camphor	NA	NA	NA	NA
<i>Cnicus benedictus</i>	Blessed thistle	NA	NA	NA	NA
<i>Commiphora myrrha</i>	Myrrh	+ 5	NA	+ 5	NA
<i>Commiphora wightii</i>	Guggul	+ 5	NA	NA	NA
<i>Convolvulus arvensis</i>	Bindweed	NA	NA	NA	NA
<i>Coptis chinensis</i>	Huanglian	+ 5	- 5	⊖ 5	⊖ 5
<i>Croton lechleri</i>	Sangre de drago	NA	NA	NA	NA
<i>Crataegus monogyna</i>	Hawthorn	+/- p	- 5	- 5	NA
<i>Curcuma longa</i>	Tumeric	⊖ 1	- 2	- 2	⊖ 5
<i>Cymbopogon citratus</i>	Lemongrass	NA	NA	NA	NA
<i>Dendranthema boreale</i>	Chrysanthemum boreale	NA	NA	NA	NA
<i>Desmodium adsensens</i>	Desmodium	NA	NA	NA	NA
<i>Dioscorea alata</i>	Purple yam	NA	NA	NA	NA
<i>Dioscorea villosa</i>	Wild yam	- 5	NA	NA	NA
<i>Echinacea purpurea</i>	Echinacea	+ 1	⊖ 1	- 2	⊖ 5
<i>Eleutherococcus senticosus</i>	Siberian Ginseng	⊖ 2	⊖ 2	NA	NA
<i>Ephedra sinica</i>	Ephedra	⊖ 2	NA	⊖ 2	NA
<i>Epimedium sagittatum</i>	Epimedium	NA	NA	NA	NA

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Eschscholzia californica</i>	Escholtzia / californica puppy	NA	NA	NA	NA
<i>Euterpe oleraceae</i>	Açaí	NA	NA	NA	NA
<i>Filipendula ulmaria</i>	Meadowsweet	NA	NA	NA	NA
<i>Fucus vesiculosus</i>	Bladder wrack	NA	NA	NA	NA
<i>Fumaria officinalis</i>	Fumitory	NA	NA	⊖ 5	NA
<i>Ganoderma lucidum</i>	Reishi mushroom	NA	NA	NA	NA
<i>Garcinia mangostana</i>	Mangosteen	- 5	- 5	- 5	- 5
<i>Geissospermum vellosii</i>	Pao pereira	NA	NA	NA	NA
Ginkgo biloba	Ginkgo	+/- C	⊖ 1	⊖ 1	- 5
<i>Glebionis coronaria</i>	Garland chrysanthemum	NA	NA	NA	NA
<i>Glehnia littoralis</i>	Glehnia	NA	NA	NA	NA
Glycine max	Soy extracts	+ 3	⊖ 2	- 3	- 5
Glycyrrhiza glabra	Licorice (liquorice)	+ 1	- 5	+ 5	- 5
<i>Griffonia simplicifolia</i>	Griffonia	NA	NA	NA	NA
<i>Grifola frondosa</i>	Maitake	NA	NA	NA	NA
<i>Gynura nepalensis</i>	Cholesterol spinach	NA	NA	NA	NA
<i>Handroanthus impetiginosus</i>	Lapacho	NA	NA	NA	NA
<i>Harpagophytum procumbens</i>	Devil's claw (African)	⊖ 5	⊖ 5	⊖ 5	NA
<i>Hedera helix</i>	English ivy	⊖ 5	- 5	⊖ 5	- 5
<i>Hedeoma pulegioides</i>	American pennyroyal	NA	NA	NA	NA
<i>Hoodia gordonii</i>	Hoodia	- 5	⊖ 5	⊖ 5	NA
<i>Humulus lupulus</i>	Hops	⊖ 5	⊖ 5	- 5	⊖ 5
<i>Huperzia serrata</i>	Huperzia	+ 5	⊖ 5	+ 5	NA
Hydrastis canadensis	Goldenseal	- 1	- 1	⊖ 2	- 5
Hypericum perforatum	Saint John's wort	+ 1	⊖ 1	⊖ 1	+ 2
<i>Ilex paraguariensis</i>	Mate	NA	NA	NA	NA
<i>Indigofera tinctoria</i>	True indigo	NA	NA	NA	NA
<i>Inonotus obliquus</i>	Chaga mushroom	NA	NA	NA	NA
<i>Irvingia gabonensis</i>	African mango	NA	NA	NA	NA
<i>Isatis tinctoria</i>	Woad	NA	NA	NA	NA
<i>Larrea divaricata</i>	Chaparral (Jarrila)	NA	NA	NA	NA
<i>Larrea tridentata</i>	Chaparral (Creasote bush)	NA	NA	NA	NA
<i>Lavandula angustifolia</i>	Lavender	⊖ 2	⊖ 2	⊖ 2	NA
<i>Lepidium meyenii</i>	Maca	NA	NA	NA	NA
<i>Lentinula edodes</i>	Shiitake	NA	NA	NA	NA
<i>Ligustrum lucidum</i> Ait	Ligustrum lucidum	NA	NA	NA	NA

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Linum usitatissimum</i>	Flaxseed	NA	NA	NA	NA
<i>Lobelia inflata</i>	Lobelia	NA	NA	NA	NA
<i>Lycium barbarum</i>	Goji	+/- p	- 5	- 5	NA
<i>Magnolia officinalis</i>	Magnolia	⊖ 5	⊖ 5	- 5	⊖ 5
<i>Marrubium vulgare</i>	Horehound (white)	NA	NA	NA	NA
<i>Matricaria recutita</i>	Chamomile (German)	- 4	- 5	- 4	NA
<i>Medicago sativa</i>	Alfalfa	NA	NA	NA	NA
<i>Medusomyces gisevii</i>	Kombucha	NA	NA	NA	NA
<i>Melaleuca alternifolia</i>	Tea tree oil	NA	NA	NA	NA
<i>Melilotus officinalis</i>	Melilotus	NA	NA	NA	NA
<i>Melissa officinalis</i>	Lemon balm	NA	NA	NA	NA
Mentha piperita	Peppermint	- 2	- 5	⊖ 2	NA
<i>Mentha pulegium</i>	Pennyroyal (European)	NA	NA	NA	NA
<i>Morinda citrifolia</i>	Noni	- 4	NA	- 5	NA
<i>Momordica charantia</i>	Bitter melon	NA	NA	NA	NA
<i>Monascus purpureus</i>	Red yeast rice	⊖ 2	⊖ 5	⊖ 5	⊖ 5
<i>Moringa oleifera</i>	Moringa	- 4	⊖ 5	NA	NA
<i>Myrcaria dubia</i>	Camu-camu	NA	NA	NA	NA
<i>Nerium oleander</i>	Oleander	NA	NA	NA	NA
Nigella sativa	Black seed	- 2	- 2	NA	NA
<i>Oenothera biennis</i>	Evening primrose	⊖ 5	⊖ 5	⊖ 5	NA
<i>Oldenlandia (hedyotis) diffusa</i>	Herba Oldenlandiae	+ 5	NA	NA	NA
<i>Olea europaea</i>	Olive tree	⊖ 5	⊖ 5	⊖ 5	⊖ 5
<i>Ophiocordyceps sinensis</i>	Cordyceps	NA	NA	NA	NA
Panax ginseng	Ginseng (asian)	+ 2	- 3	⊖ 1	⊖ 3
<i>Panax notoginseng</i>	Notoginseng	⊖ 4	⊖ 5	+ 5	NA
<i>Panax quinquefolius</i>	Ginseng (american)	⊖ 5	NA	⊖ 5	NA
<i>Passiflora incarnata</i>	Passionflower	NA	NA	NA	NA
<i>Paullinia cupana</i>	Guarana	NA	NA	NA	NA
<i>Pausinystalia johimbe</i>	Yohimbe	NA	- 5	NA	NA
<i>Pelargonium sidoides</i>	Umckaloabo	NA	NA	NA	NA
<i>Petasites hybridus</i>	Butterbur	NA	NA	NA	NA
<i>Petiveria alliacea</i>	Guinea henweed	- 5	⊖ 5	- 5	NA
<i>Peumus boldus</i>	Boldo	NA	NA	NA	NA
<i>Phellinus linteus</i>	Black hoof medicinal mushroom	NA	NA	NA	NA
<i>Piper methysticum</i>	Kava kava	⊖ 1	⊖ 1	⊖ 2	NA
<i>Piper nigrum</i>	Black pepper	- 5	- 5	NA	NA
<i>Phyllanthus emblica</i>	Emblica	NA	NA	NA	NA
<i>Phytolacca americana</i>	Pokeweed	NA	NA	NA	NA

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Pinus maritima</i>	Pine bark	NA	NA	NA	NA
<i>Plectranthus barbatus</i>	Indian coleus	NA	NA	NA	NA
<i>Prunus africana</i>	Pygeum	NA	NA	NA	NA
<i>Pleurotus ostreatus</i>	Oyster mushroom	NA	NA	NA	NA
<i>Pueraria lobata</i>	Kudzu	+ 5	- 3	+ 3	NA
<i>Punica granatum</i>	Pomegranate	⊖ 1	NA	- 5	NA
<i>Raphanus sativus</i> L. var <i>niger</i>	Black radish	⊖ 5	NA	+ 4	NA
<i>Rhamnus purshiana</i>	Cascara	+ 5	NA	NA	NA
<i>Rheum palmatum</i>	Rhubarb	+ 4	+ 5	⊖ 5	NA
<i>Rhodiola rosea</i>	Rhodiola	⊖ 2	⊖ 2	⊖ 2	NA
<i>Rosmarinus officinalis</i>	Rosemary	+ 5	NA	NA	NA
<i>Rumex acetosella</i>	Sorrel	NA	NA	NA	NA
<i>Ruscus aculeatus</i>	Butcher's broom	NA	NA	NA	NA
<i>Salix alba</i>	Willow bark	+ 5	NA	NA	NA
<i>Salvia divinorum</i>	Salvia	NA	NA	NA	NA
<i>Salvia hispanica</i>	Chia	NA	NA	NA	NA
<i>Sambucus nigra</i>	Elderberry	⊖ 5	⊖ 5	⊖ 5	NA
<i>Sanguinaria canadensis</i>	Bloodroot	NA	NA	NA	NA
<i>Sarcandra glabra</i>	Herba Sarcandrae	NA	NA	NA	NA
<i>Sassafras albidum</i>	Sassafras	NA	NA	- 5	NA
<i>Scaevola spinescens</i>	Maroon bush	NA	NA	NA	NA
<i>Schisandra chinensis</i>	Wuweizi	+ 4	- 5	- 5	NA
<i>Schisandra sphenanthera</i>	Wuzhi	- 1	NA	- 5	NA
<i>Scutellaria baicalensis/barbata</i>	Baikal skullcap / barbed skullcap	⊖ 1	⊖ 2	⊖ 1	⊖ 5
<i>Serenoa repens</i>	Saw palmetto	⊖ 1	⊖ 1	⊖ 2	- 5
<i>Silybum marianum</i>	Milk thistle	⊖ 1	⊖ 1	⊖ 1	⊖ 5
<i>Smilax glabra</i>	Sarsaparilla (chinese) / Tu Fu Ling	NA	NA	NA	NA
<i>Sophora flavescens</i>	Ku Shen Gen	+ 4	- 5	+/- p	NA
<i>Stevia rebaudiana</i>	Stevia	+/- p	⊖ 5	+ 5	NA
<i>Stillingia sylvatica</i>	Stillingia	NA	NA	NA	NA
<i>Sutherlandia frutescens</i>	Sutherlandia	+ 4	⊖ 5	- 5	- 5
<i>Symphytum officinale</i>	Comfrey	NA	NA	NA	NA
<i>Synsepalum dulcificum</i>	Miracle fruit	NA	NA	NA	NA
<i>Tanacetum parthenium</i>	Feverfew	- 5	- 5	- 5	NA
<i>Taraxacum officinale</i>	Dandelion	⊖ 3	⊖ 5	- 5	⊖ 5
<i>Thymus vulgaris</i>	Thyme	⊖ 5	NA	NA	NA
<i>Trametes versicolor</i>	Turkey tail mushroom	NA	NA	NA	NA
<i>Tribulus terrestris</i>	Caltrop	NA	NA	NA	NA
<i>Trifolium pratense</i>	Red clover	⊖ 4	- 5	- 5	⊖ 5

Plant name (Latin name)	Common name	Cytochrome			
		3A4	2D6	1A2	2C8
<i>Trigonella foenum-graecum</i>	Fenugreek	⊖ 2	⊖ 2	NA	NA
<i>Triticum aestivum</i>	Wheat grass	NA	NA	NA	NA
<i>Turnera diffusa</i>	Damiana	NA	NA	NA	NA
<i>Ulmus rubra</i>	Slippery elm	NA	NA	NA	NA
<i>Uncaria tomentosa</i>	Cat's claw	- 4	NA	NA	NA
<i>Urtica dioica</i>	Nettle	- 5	NA	NA	NA
<i>Vaccinium corymbosum</i>	Blueberry (American)	⊖ 2	NA	NA	NA
<i>Vaccinium macrocarpon</i>	Cranberry	- 2	⊖ 5	⊖ 2	- 5
<i>Vaccinium myrtillus</i>	Bilberry	NA	NA	NA	NA
<i>Valeriana officinalis</i>	Valerian	⊖ 1	⊖ 1	⊖ 2	⊖ 5
<i>Viscum album</i>	Mistletoe	- 5	NA	NA	NA
<i>Vitis vinifera</i>	Grape	- 4	⊖ 2	+ 2	- 5
<i>Vitex agnus-castus</i>	Chasteberry	- 5	- 5	- 5	NA
<i>Withania somnifera</i>	Ashwagandha	- 5	⊖ 5	⊖ 5	NA
<i>Zingiber officinale</i>	Ginger	+/- p	⊖ 4	+/- p	- 5

Dietary supplements

Dietary supplement name	Cytochrome			
	3A4	2D6	1A2	2C8
Alpha-lipoic acid	NA	NA	NA	NA
Arginine	NA	NA	NA	NA
Beta-carotene	+ 5	NA	+/- p	NA
Beta-elemene	NA	NA	NA	NA
Beta-Hydroxy beta-methylbutyric acid	NA	NA	NA	NA
Biotin	NA	NA	⊖ 5	NA
Bromelain	NA	NA	NA	NA
Calcium-D-glucarate	NA	NA	NA	NA
Capsaicin	+/- p	⊖ 5	- 5	NA
Cesium chloride	NA	NA	NA	NA
Chitosan / Deacetylated chitin	- 4	NA	NA	NA
Chondroitine	NA	NA	NA	NA
Chromium picolinate	NA	NA	NA	NA
Colostrum (bovine)	NA	NA	NA	NA
Conjugated linoleic acid	- 5	⊖ 5	- 5	NA
Diindolylmethane	+ 4	NA	+ 2	NA

Dietary supplement name	Cytochrome			
	3A4	2D6	1A2	2C8
Dimethylglycine	NA	NA	NA	NA
Dimethylsulfoxide	- 4	NA	- 5	NA
D-limonene	⊖ 5	⊖ 5	NA	NA
Ellagic acid	- 5	- 5	NA	NA
Genistein Combined Polysaccharide	NA	NA	NA	NA
Germanium	NA	NA	NA	NA
Glucosamine	⊖ 5	⊖ 5	⊖ 5	NA
Glutamine	NA	NA	NA	NA
Glyconutrient	NA	NA	NA	NA
Hydrazine monosulfate	NA	NA	NA	NA
Inositol hexakisphosphate	NA	NA	NA	NA
Leucine	NA	NA	NA	NA
Levocarnitine	NA	NA	⊖ 5	NA
L-theanine	NA	NA	NA	NA
Lutein	⊖ 5	⊖ 5	⊖ 5	⊖ 5
Lycopene	⊖ 4	⊖ 5	NA	NA
Manuka honey	NA	NA	NA	NA
MGN-3	NA	NA	NA	NA
Modified Citrus Pectin	NA	NA	NA	NA
N-Acetylcysteine	NA	NA	NA	NA
Nattokinase	⊖ 5	NA	NA	NA
Nicotinamide	NA	NA	NA	NA
Omega-3	- 5	NA	- 5	NA
Palladium-alpha-lipoic acid complex	NA	NA	NA	NA
Perillyl alcohol	NA	NA	NA	NA
Piperine	+/- C	- 5	- 5	NA
Pollen extract	NA	⊖ 5	- 5	NA
Probiotics (bacteria mixture)	NA	NA	- 5	NA
Probiotics: E Coli Nissle 1917	- 5	NA	+ 5	NA
Propolis	⊖ 5	⊖ 5	- 5	NA
ProtoceI	NA	NA	NA	NA
Psyllium	NA	NA	NA	NA

Dietary supplement name	Cytochrome			
	3A4	2D6	1A2	2C8
Pteroylglutamic acid	NA	NA	NA	NA
Pyridoxal phosphate	NA	NA	NA	NA
Quercetin	- 2	- 5	- 5	⊖ 2
Resveratrol	- 1	- 2	+ 2	- 5
Royal jelly	NA	NA	NA	NA
S-adenosylmethionine	NA	NA	NA	NA
Selenium	NA	- 5	NA	NA
Shark cartilage	NA	NA	NA	NA
Squalamine	NA	NA	NA	NA
Sulfated alpha-L-fucan	⊖ 2	⊖ 2	NA	NA
Superoxide dismutase	NA	NA	NA	NA
Taurine	⊖ 5	NA	NA	NA
Ubiquinone	NA	NA	NA	NA
Usnic acid	⊖ 5	- 5	⊖ 5	- 5
Vinpocetine	- 5	- 5	⊖ 5	NA
Vitamin A	- 5	- 5	⊖ 5	⊖ 5
Vitamin B12	- 5	NA	NA	NA
Vitamin C	⊖ 1	NA	+ 5	NA
Vitamin D	⊖ 2	⊖ 5	⊖ 5	- 5
Vitamin E	- 3	⊖ 3	- 5	NA
Vitamin O	NA	NA	NA	NA
Wheat germ extracts	NA	NA	NA	NA
Zeolite	NA	NA	NA	NA
Zinc	NA	NA	NA	NA

Food

Food name	Cytochrome			
	3A4	2D6	1A2	2C8
Açaí	NA	NA	NA	NA
Beer	⊖ 3	NA	⊖ 5	NA
Black radish	⊖ 5	NA	+ 4	NA
Blueberry (American)	⊖ 2	NA	NA	NA
Cranberry	- 2	⊖ 5	⊖ 2	- 5

Food name	Cytochrome			
	3A4	2D6	1A2	2C8
Coffee	⊖ 2	NA	- 2	NA
Grapefruit	- 1	⊖ 1	- 2	NA
Green tea	- 3	⊖ 1	⊖ 1	- 5
Guarana	NA	NA	NA	NA
Licorice (liquorice)	+ 1	- 5	+ 5	- 5
Lime	- 3	NA	NA	NA
Mangosteen	- 5	- 5	- 5	- 5
Noni	- 4	NA	- 5	NA

Food name	Cytochrome			
	3A4	2D6	1A2	2C8
Papaya	⊖ 5	NA	⊖ 5	NA
Pomegranate	⊖ 1	NA	- 5	NA
Pomelo	- 3	NA	NA	NA
Red wine	⊖ 2	NA	NA	NA
Seville orange	- 1	⊖ 2	⊖ 2	NA
Soy	+ 3	⊖ 2	- 3	- 5
Star fruit (Carambola)	- 4	NA	NA	NA
Tomato juice	- 4	NA	⊖ 5	NA

About 50% of the 261 HFDS could be classified as inducer, inhibitor, or having no interaction with CYP3A4. About 50% of anticancer drugs are substrates of CYP3A4 and are the main source of pharmacokinetic interactions. Sixteen HFDS were found to inhibit CYP3A4 in at least one clinical trial (Table 6), and could, therefore, be often involved in potential drug-HFDS interactions. Six were inducers of CYP3A4, and 2 were either inducers or inhibitors in different trials (gingko and piperine). Very few data were available for CYP2C8: only one clinical trial (quercetin) and some *in vitro* assays (31/161=12%). Most of the identified interactions were inhibitions. Details are available in Supplementary Figure 1 and 2.

Table 6: Substances with clinically relevant interaction with CYP3A4 probes (either induction or inhibition). Concomitant use of these complementary alternative medicines or diet can lead to increased toxicity (CYP3A4 inhibition) or decreased efficacy (CYP3A4 induction). FDA guidelines for drug-drug interactions [197] were used to differentiate the strength of the interaction between HFDS and cytochromes and could be strong/moderate or mild.

	CYP3A4 Inhibitor	CYP3A4 Inducers	CYP3A4 Inhibitor & Inducer
strong/moderate interaction	Grapefruit (<i>Citrus paradisi</i>) [60–78,24,79,23,80–84]	Saint-John's wort (<i>Hypericum perforatum</i>) [29,30,53,54,122–133]	
	Sevilla orange (<i>Citrus aurantium</i>) [198,199]		
	Goldenseal (<i>Hydrastis canadensis</i>) [47,119,120]		
mild interaction	Lime (<i>Citrus arantifolia</i>) [200]	Ginseng (<i>Panax ginseng</i>) [150]	Ginkgo (<i>Ginkgo biloba</i>) [107,109]
	Cranberry (<i>Vaccinium macrocarpon</i>) [161]	Licorice (<i>Glycyrrhiza glabra</i>) [201]	Piperine / pepper extracts (<i>Piper nigrum</i>) [202,203]
	Green tea (<i>Camellia sinensis</i>) [58]	Echinacea (<i>Echinacea purpurea</i>) [96,97]	
	Peppermint (<i>Mentha piperita</i>) [144]	Soy extracts (<i>Glycine max</i>) / genistein [114]	
	Pomelo (<i>Citrus maxima</i>) [204]		
	Black seed (<i>Nigella sativa</i>) [205]		
	Wuzhi (<i>Schisandra sphenanthera</i>) [206,207]		
	Broccoli sprouts extracts /kale/sulforaphane [208]		
	Quercetin [209]		
	Vitamin E [210]		
	Resveratrol [211,212]		

4. Discussion

4.1. General considerations for herb-drug interactions

Herbs and dietary supplements contain xenobiotics that are absorbed to exert biological activity. Therefore, they are subject to HFDI with the same mechanisms as drug-drug interaction, which have been extensively described in oncology [213–215]. There are two main types of drug-drug interactions: pharmacokinetic interactions, where one of the drugs affects the concentration of the other; and pharmacodynamic interactions when the two drugs have an additive, synergistic or antagonistic effect or have the same target.

Phase 1 oxidative metabolism via cytochromes is the main biotransformation process for many oncology drugs. Numerous drugs inhibit or induce CYPs, which play a major role in the disposition kinetics of some oncology drugs. Some drugs like cyclophosphamide are prodrugs and require metabolic activation to exert their effects. The role of CYP3A4 has been extensively studied with most oncology drugs (Table 2 and Supplementary Table 2).

This research focused on cytochrome interactions and does not take into account other pharmacokinetic mechanisms, like absorption, or pharmacodynamics interactions.

A limitation of our work is that despite a systematic approach, this review is a scoping review and not a systematic review and is not following Prisma criteria. [216]

4.2. Relevance and limitations of *in vitro* assays

Most studies of plant-drug interactions are *in vitro* assays and have numerous limitations. Mostly, the inhibition/binding of plant extracts (aqueous, ethanolic, or methanolic) was directly assessed on-targets (microsomes or PXR or cell lines). This model does not take into account the complex mechanisms of absorption: molecules responsible for *in vitro* inhibition are not necessarily absorbed, and their bioavailability could be low or null.

In the case of Saint John's wort, the herb-drug interaction is driven by the concentration of hyperforin, which is responsible for CYP3A4 induction. However, in most cases, there are several active phytochemicals and alkaloids within the same plant, and they are not always identified. The method of extraction of an alkaloid could also bring a lot of variation. Furthermore, their maximal plasma concentration achieved by oral ingestion is largely unknown and is not available for most herbs. Considering the variability of methodologies that have been used by different researches, we considered an *in vitro* interaction as relevant when the interaction was deemed significant by the authors. There are examples of molecules for which the cytochrome-interacting component has been identified, and its pharmacokinetics in human is well-known, such as hyperforin for Saint John's wort [217]. Interactions with Grapefruit (*Citrus Paradisi*) and cytochromes have been extensively described, and the role of different components appears to be more complex. Bergamottin, one of the furanocoumarin components of grapefruit, is a clinically meaningful CYP3A4 inhibitor [73]. However, Bergamottin is not the only furanocoumarin responsible for grapefruit-induced inhibition of CYP3A4. Moreover, CYP3A4 inhibition could also occur in the lining of the intestines rather than within the liver [218], and a component that is not absorbed could still be responsible for a drug interaction by increasing its bioavailability. Although the C_{max}/IC_{50} ratio is very relevant to predict drug-drug interactions, this is less true for herb-drug interactions for the above-mentioned reasons, which is why this approach has not been chosen. Further investigations on the relevance of *in vitro* studies to predict herb-drug interactions are strongly needed.

Nevertheless, when *in vitro* assays found no interaction with cytochromes, it is unlikely that the plant extracts will interact when taken orally. These trials could therefore have a good negative predictive value.

4.3. Relevance and limitations of animal assays

Humans and mice share 97.5% of their DNA. However, rat's orthologues of CYP2C human cytochromes (CYP2C6, 2C7, 2C11, 2C12, 2C13, 2C22, and 2C23), and CYP3A (3A1, 3A2, 3A9, CYP2C18, 3A23, and 3A62) do not always share the same substrates affinities as human CYP [219–221]. Moreover, drug doses and HFDS doses in the rat are difficult to transpose to humans [222]. Still, bioavailability is taken into account in this model.

As an example, pomegranate juice significantly inhibits CYP2C9 and CYP3A4 in preclinical models [223]. However, 5 human clinical trials do not confirm this inhibition [76,80,224,225]. Similarly, *in vitro* inhibition of CYP3A4 by coffee does not have an impact on felodipine pharmacokinetics, a CYP3A4 probe, in healthy volunteers [81].

4.5. Dose considerations

Most plant extracts inhibiting CYP have a concentration-dependent effect [6,110,143] and induction of CYP3A4 is likely dose-dependent [226]. Xiao *et al.* found that 1g per day of genistein, an isoflavonoid found in soy, given for 15 days, significantly induces CYP3A4 [114] (AUC decrease of midazolam of 20%). In the Asian population, daily intakes of genistein would not exceed 10mg per day, which is 100 times lower than the amount tested in Xiao's trial. Some soy extracts could have a much higher amount (>100mg per pill) [227].

Similarly, grape and particularly its skin, contains (trans-)resveratrol, which significantly modifies buspirone and carbamazepine PK by inhibition of CYP3A4 [212,228], inhibits CYP2D6 [228] and induces CYP1A2 [228] at a dose of 1g per day. Red wine contains an average amount of about 1mg/L of resveratrol [229], and it would need 800kg of grape to have an intake of 1g of resveratrol [230]. The effect of resveratrol on CYP3A4 is small, with a modification of AUC of around 20% of CYP3A4 probes [212,228]. Thus, no clinically significant interaction is expected when resveratrol doses are 100-1000 times lower.

4.6. Illustration of the complexity of the prediction of interactions through examples

Because of the complexity of HFDS interactions, simplifications were made. Some HFDS such as curcumin or green tea are widely used, and the results given in Table 4 and 5 requires clarification.

4.6.1 Curcumin

Curcumin is often used for its antioxidant properties, in combination with piperine, which enhances the absorption of curcuminoids. Volak and colleagues [91] studied the influence of a combination of curcuminoids with piperine, on midazolam PK, taken two days later. This trial was not designed to assess CYP3A4 induction: CYP3A4 induction via activation of the pregnane X receptor needs several weeks [231,232] (although a strong effect, like CYP3A4 induction by phenytoin, could be detected earlier [233]). Two other studies [92,93] were done with concomitant intakes of curcumin and CYP3A4 probes. Mir and colleagues [18] described two cases of interaction between curcumin plus piperine and everolimus. The chronological imputability criteria [15] was maximal since rechallenging had the same effect on everolimus plasma concentrations. However, this induction is probably due to piperine and not curcumin, since piperine has demonstrated some CYP3A4 inducing properties [202,203] in a clinical trial. Overall, curcumin extracts should be avoided in association with piperine when there is a risk of interaction through CYP3A4. Curcumin alone seems safe, although a clinical trial designed to assess induction is needed.

4.6.2 Greentea

Tea is the most consumed beverage on earth, and green tea is prevalent, particularly among the Asian population [234]. Contrary to black tea, green tea contains more EGCG, due to different processing of *Camellia sinensis* leaves. In a trial with 42 patients, Chow and colleagues [58] found that a dose of 800mg of EGCG increased buspirone AUC by 20% (CYP3A4 probe). Eight hundred mg of EGCG is equivalent to 8 to 16 cups of green tea, depending on the quality and infusion methods of the tea. Black tea contains 20 times lower amounts of EGCG [235]. Consumption of a large amount of tea is not rare, and regular consumption of green tea could increase the concentrations of a drug metabolised by CYP3A4.

4.7 Limitations of the research

4.7.1 Variability of phytotherapy formulation

An important limitation to this research is that the studied phytotherapies could come from different sources (*e.g.*, whole plant vs. leaves). Different preparations from different brands might have various concentrations of active substances. However, we found 25 trials assessing CYP inhibition with grapefruit and 24 found a significant inhibition of CYP3A4. Similarly, 14 trials tested CYP3A4 induction with different formulations of Saint-John's wort, and 12 found a significant induction, suggesting that strong induction or inhibition of CYP can be found independently of dosage form or providers.

4.7.2 Extrapolation of the results to predict HFDS-drug interactions

The potential of a herb-drug interaction depends on the extent to which that drug is metabolised by a particular CYP enzyme. In case of a minor contribution of CYP3A4, risks of HFDS interactions may be overestimated. Factors such as the quality of the product, the plant extract used to make the pill, the dose taken by the patient are making this prediction even more difficult. Also, the tested herbal dose and interproduct variability in phytochemical content complicates the extrapolation of *in vitro* and clinical data with non-anticancer drugs.

However, anticancer drugs have a small therapeutic index, and a 20% modification of the dose or the AUC of the drug could lead to a substantial increase in the toxicity.

4.7.3 Pharmacodynamic interactions

Pharmacodynamic interactions have not been explored in this review and should also be considered. For example, white willow extracts (*Salix Alba*) [236], which contain aspirin-like salicylates, increase bleeding risk, and the effect could be synergistic with treatments that induce thrombocytopenia (carboplatin among others). Despite a clinically proven absence of kava kava (*Piper methysticum*) interaction with cytochromes, this herb contains pipermethysticin and other kava lactone potentially

responsible for liver injuries [237–239]. The FDA now advises consumers on the potential risk of severe liver injury associated with the use of kava [237].

Increased toxicity risk of anticancer drugs by HFDS could also be a concern and should be kept in mind even when no cytochrome interaction is expected.

4.8. Recommendations for clinicians and pharmacists

The concomitant use of grapefruit and Saint John's wort with CYP3A4 substrates is a well-known source of interactions. Such interactions were confirmed by anticancer-HFDS interaction studies and cytochrome P-450-specific studies (Table 3). Their concomitant use with known or possible CYP3A4-metabolised anticancer drugs should, therefore, be strongly discouraged.

Similarly, patients receiving treatments metabolised by CYP3A4 that have a narrow therapeutic index should avoid regular consumption of other HFDS shown in Table 6. These substances are likely to modify the AUC of the anticancer drug and could lead to increased toxicity or underdosing.

Grade 1 and grade 2 interactions on the 5-level scale should be avoided. Grade 4 and 5 interactions are based on preclinical data which have a low level of confidence, and no change in dosage is recommended. Grade 3 interactions are mild or unlikely and should not lead to clinical change. However, they should be considered in case of unexpected clinical events such as increased toxicity or tumour progression without any adverse events which could be due to underdosage.

Other cytochrome-mediated interaction can be anticipated using data from Tables 3 and 5. A strong level of evidence for cytochrome-mediated interaction, which is from 1 to 3 on the scale shown in Table 1, should lead clinicians to propose the withdrawal of the HFDS due to the potential risk of interaction with the anticancer drug.

In most drug-drug interaction guidelines, such as Lexicomp®, which is a tool for drug interaction analyses, an interaction considered mild according to FDA guidelines is not considered clinically significant. Similarly, when a weaker CYP inducer and a substrate drug are matched, which corresponds in our scale to a grade 3 interaction, no change in clinical practice should be recommended.

However, the 5-level scale assessing the amount of evidence to hierarchize the probability of an interaction between a HFDS and an anticancer drug was constructed for the purpose of this study and has not been validated elsewhere. Its relevance should be confirmed in further studies. Therefore, when no or few data is available on an interaction, caution should be taken about potential unexplored interactions, and patients should be warned of potential risks of increased toxicity or decreased efficacy.

5. Conclusions

We conducted an extensive review to analyse potential pharmacokinetic interactions with herbs, food and dietary supplements. CYP3A4, CYP2D6, CYP1A2, and CYP2C8 are the main cytochromes involved in the metabolism of anticancer drugs. Numerous HFDS were found to significantly inhibit or induce CYP3A4 in clinical trials. We generated a ready-to-use table that synthesises current knowledge on possible interactions between herbs drugs and dietary supplements that could involve inhibition or induction of cytochromes. Clinicians and patients should be aware of these potential sources of treatment failure and adverse events.

Funding: no funding

Disclosure:

Paul Gougis, Marc Hilmi, Christian Funck-Brentano declare no conflict of interests.

Olivier Mir is a consultant for Amgen, Astra-Zeneca, Bayer, Blueprint Medicines, Bristol Myers-Squibb, Eli-Lilly, Incyte, Ipsen, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, Vifor Pharma; board membership for Amgen, Astra-Zeneca, Bayer, Blueprint Medicines, Bristol Myers-Squibb, Eli-Lilly, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, Vifor Pharma; speaker bureau of Eli-Lilly, Roche, Servier; stock ownership of Amplitude surgical, Transgene and employee of Gustave Roussy and ESMO (Annals of Oncology)

Arthur Geraud: As part of the Drug Development Department (DITEP) Principal/sub-Investigator of Clinical Trials for Abbvie, Adaptimmune, Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, Astra Zeneca Ab, Aveo, Bayer Healthcare Ag, Bbb Technologies Bv, Beigene, Bioalliance Pharma, Biontech Ag, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Bristol-Myers Squibb International Corporation, Ca, Celgene Corporation, Cephalon, Chugai Pharmaceutical Co., Clovis Oncology, Cullinan-Apollo, Daiichi Sankyo, Debiopharm S.A., Eisai, Eisai Limited, Eli Lilly, Exelixis, Forma Therapeutics, Gamamabs, Genentech, Gilead Sciences, Glaxosmithkline, Glenmark Pharmaceuticals, H3 Biomedicine, Hoffmann La Roche Ag, Incyte Corporation, Innate Pharma, Institut De Recherche Pierre Fabre, Iris Servier, Janssen Cilag, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharm. Dev., Lilly France, Loxo Oncology, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Kgaa, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Nerviano Medical Sciences, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncomed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Ose Pharma, Pfizer, Pharma Mar, Philogen S.P.A., Pierre Fabre Medicament, Plexxikon, Rigontec Gmbh, Roche, Sanofi Aventis, Sierra Oncology, Sotio A.S, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Tioma Therapeutics, Wyeth Pharmaceuticals France, Xencor, Y's Therapeutics, Research Grants from Astrazeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi. Non-financial support (drug supplied) from Astrazeneca, Bayer, BMS, Boringher Ingelheim, Johnson & Johnson, Lilly, Medimmune, Merck, NH TherAGuiX, Pfizer, Roche.

References

- [1] M. Rashrash, J.C. Schommer, L.M. Brown, Prevalence and Predictors of Herbal Medicine Use Among Adults in the United States, *J Patient Exp.* 4 (2017) 108–113. <https://doi.org/10.1177/2374373517706612>.
- [2] J. Tilburt, T. Kaptchu, WHO | Herbal medicine research and global health: an ethical analysis, WHO. (n.d.). <http://www.who.int/bulletin/volumes/86/8/07-042820/en/> (accessed December 5, 2018).
- [3] G.K. Dy, L. Bekele, L.J. Hanson, A. Furth, S. Mandrekar, J.A. Sloan, A.A. Adjei, Complementary and alternative medicine use by patients enrolled onto phase I clinical trials, *J. Clin. Oncol.* 22 (2004) 4810–4815. <https://doi.org/10.1200/JCO.2004.03.121>.
- [4] P. Posadzki, L. Watson, E. Ernst, Herb-drug interactions: an overview of systematic reviews, *Br J Clin Pharmacol.* 75 (2013) 603–618. <https://doi.org/10.1111/j.1365-2125.2012.04350.x>.
- [5] T.M. Bush, K.S. Rayburn, S.W. Holloway, D.S. Sanchez-Yamamoto, B.L. Allen, T. Lam, B.K. So, D.H. Tran, E.R. Greyber, S. Kantor, L.W. Roth, Adverse interactions between herbal and dietary substances and prescription medications: a clinical survey, *Altern Ther Health Med.* 13 (2007) 30–35.
- [6] S. Engdal, O. Klepp, O.G. Nilsen, Identification and exploration of herb-drug combinations used by cancer patients, *Integr Cancer Ther.* 8 (2009) 29–36. <https://doi.org/10.1177/1534735408330202>.
- [7] L. Alnaim, Therapeutic drug monitoring of cancer chemotherapy, *J Oncol Pharm Pract.* 13 (2007) 207–221. <https://doi.org/10.1177/1078155207081133>.
- [8] C. for D.E. and Research, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry, U.S. Food and Drug Administration. (2019). <http://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-metabolism-and-transporter-mediated-drug-drug-interaction-studies-guidance-industry> (accessed July 9, 2019).
- [9] C. for D.E. and Research, Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry, U.S. Food and Drug Administration. (2019). <http://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-study-design-data-analysis-and-clinical-implications-guidance> (accessed July 9, 2019).
- [10] Anonymous, Investigation of drug interactions, European Medicines Agency. (2018). <https://www.ema.europa.eu/en/investigation-drug-interactions> (accessed July 9, 2019).
- [11] Drugs@FDA: FDA Approved Drug Products, (n.d.). <https://www.accessdata.fda.gov/scripts/cder/daf/> (accessed February 9, 2018).
- [12] DailyMed, (n.d.). <https://dailymed.nlm.nih.gov/dailymed/> (accessed November 29, 2018).
- [13] Home - MICROMEDEX, (n.d.). <https://www.micromedexsolutions.com/micromedex2/librarian> (accessed November 29, 2018).
- [14] About Herbs, Botanicals & Other Products | Memorial Sloan Kettering Cancer Center, (n.d.). <https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs> (accessed January 19, 2021).
- [15] Y. Arimone, I. Bidault, J.-P. Dutertre, M. Gérardin, C. Guy, F. Haramburu, D. Hillaire-Buys, C. Meglio, C. Penfornis, H. Théophile, M.-B. Valnet-Rabier, Cercle de Réflexion sur l'Imputabilité

- (CRI), Updating the French method for the causality assessment of adverse drug reactions, *Therapie*. 68 (2013) 69–76. <https://doi.org/10.2515/therapie/2013016>.
- [16] F. Engels, de J. Fa, S. A, M. Ra, L. Wj, K. Jj, de B. P, V. J, M. Rh, Medicinal Cannabis Does Not Influence the Clinical Pharmacokinetics of Irinotecan and Docetaxel, *The Oncologist*. (2007). <https://doi.org/10.1634/theoncologist.12-3-291>.
- [17] K.G.A.M. Husaarts, D.P. Hurkmans, E. Oomen-de Hoop, L.J. van Harten, S. Berghuis, R.J. van Alphen, L.E.A. Spierings, Q.C. van Rossum-Schornagel, M.B. Vastbinder, R.H.N. van Schaik, T. van Gelder, A. Jager, R.W.F. van Leeuwen, R.H.J. Mathijssen, Impact of Curcumin (with or without Piperine) on the Pharmacokinetics of Tamoxifen, *Cancers (Basel)*. 11 (2019). <https://doi.org/10.3390/cancers11030403>.
- [18] O. Mir, S. Ropert, A.N. Chamseddine, A. Paci, Curcumin dietary supplements and everolimus-based cancer treatment, *Ann. Oncol.* 29 (2018) 287–288. <https://doi.org/10.1093/annonc/mdx714>.
- [19] A.K.L. Goey, I. Meijerman, H. Rosing, J.A. Burgers, M. Mergui-Roelvink, M. Keessen, S. Marchetti, J.H. Beijnen, J.H.M. Schellens, The effect of Echinacea purpurea on the pharmacokinetics of docetaxel, *Br J Clin Pharmacol.* 76 (2013) 467–474. <https://doi.org/10.1111/bcp.12159>.
- [20] M.C. Cox, J. Low, J. Lee, J. Walshe, N. Denduluri, A. Berman, M.G. Permenter, W.P. Petros, D.K. Price, W.D. Figg, A. Sparreboom, S.M. Swain, Influence of garlic (*Allium sativum*) on the pharmacokinetics of docetaxel, *Clin. Cancer Res.* 12 (2006) 4636–4640. <https://doi.org/10.1158/1078-0432.CCR-06-0388>.
- [21] V. B, R. J, P. T, B. A, P.-R. Jj, Effect of Grapefruit Juice on the Pharmacokinetics of Docetaxel in Cancer Patients: A Case Report, *British Journal of Clinical Pharmacology*. (2011). <https://doi.org/10.1111/j.1365-2125.2011.04052.x>.
- [22] S. Reif, M.C. Nicolson, D. Bisset, M. Reid, C. Kloft, U. Jaehde, H.L. McLeod, Effect of grapefruit juice intake on etoposide bioavailability, *Eur. J. Clin. Pharmacol.* 58 (2002) 491–494. <https://doi.org/10.1007/s00228-002-0495-9>.
- [23] R. de Vries, J.W. Smit, P. Hellemans, J. Jiao, J. Murphy, D. Skee, J. Snoeys, J. Sukbuntherng, M. Vliegen, L. de Zwart, E. Mannaert, J. de Jong, Stable isotope-labelled intravenous microdose for absolute bioavailability and effect of grapefruit juice on ibrutinib in healthy adults, *Br J Clin Pharmacol.* 81 (2016) 235–245. <https://doi.org/10.1111/bcp.12787>.
- [24] N.P. van Erp, S.D. Baker, A.S. Zandvliet, B.A. Ploeger, M. den Hollander, Z. Chen, J. den Hartigh, J.M.C. König-Quartel, H.-J. Guchelaar, H. Gelderblom, Marginal increase of sunitinib exposure by grapefruit juice, *Cancer Chemother. Pharmacol.* 67 (2011) 695–703. <https://doi.org/10.1007/s00280-010-1367-0>.
- [25] S.-I. Kimura, S. Kako, H. Wada, K. Sakamoto, M. Ashizawa, M. Sato, K. Terasako, M. Kikuchi, H. Nakasone, S. Okuda, R. Yamazaki, K. Oshima, J. Nishida, T. Watanabe, Y. Kanda, Can grapefruit juice decrease the cost of imatinib for the treatment of chronic myelogenous leukemia?, *Leuk. Res.* 35 (2011) e11–12. <https://doi.org/10.1016/j.leukres.2010.09.014>.
- [26] N.P.H. van Erp, S.D. Baker, M. Zhao, M.A. Rudek, H.-J. Guchelaar, J.W.R. Nortier, A. Sparreboom, H. Gelderblom, Effect of milk thistle (*Silybum marianum*) on the pharmacokinetics of irinotecan, *Clin. Cancer Res.* 11 (2005) 7800–7806. <https://doi.org/10.1158/1078-0432.CCR-05-1288>.

- [27] R.H.J. Mathijssen, J. Verweij, P. de Bruijn, W.J. Loos, A. Sparreboom, Effects of St. John's wort on irinotecan metabolism, *J. Natl. Cancer Inst.* 94 (2002) 1247–1249. <https://doi.org/10.1093/jnci/94.16.1247>.
- [28] A.K.L. Goey, I. Meijerman, H. Rosing, S. Marchetti, M. Mergui-Roelvink, M. Keessen, J.A. Burgers, J.H. Beijnen, J.H.M. Schellens, The effect of St John's wort on the pharmacokinetics of docetaxel, *Clin Pharmacokinet.* 53 (2014) 103–110. <https://doi.org/10.1007/s40262-013-0102-5>.
- [29] P. Smith, J.M. Bullock, B.M. Booker, C.E. Haas, C.S. Berenson, W.J. Jusko, The influence of St. John's wort on the pharmacokinetics and protein binding of imatinib mesylate, *Pharmacotherapy.* 24 (2004) 1508–1514. <https://doi.org/10.1592/phco.24.16.1508.50958>.
- [30] R.F. Frye, S.M. Fitzgerald, T.F. Lagattuta, M.W. Hruska, M.J. Egorin, Effect of St John's wort on imatinib mesylate pharmacokinetics, *Clin. Pharmacol. Ther.* 76 (2004) 323–329. <https://doi.org/10.1016/j.clpt.2004.06.007>.
- [31] A.H. Wu, M.C. Pike, L.D. Williams, D. Spicer, C.-C. Tseng, M.I. Churchwell, D.R. Doerge, Tamoxifen, soy, and lifestyle factors in Asian American women with breast cancer, *J. Clin. Oncol.* 25 (2007) 3024–3030. <https://doi.org/10.1200/JCO.2006.10.5023>.
- [32] P. Gougis, J. Wassermann, J.P. Spano, N. Keynan, C. Funck-Brentano, J.E. Salem, Clinical pharmacology of anti-angiogenic drugs in oncology, *Crit. Rev. Oncol. Hematol.* 119 (2017) 75–93. <https://doi.org/10.1016/j.critrevonc.2017.08.010>.
- [33] X. Zhang, J. Liu, F. Ye, S. Ji, N. Zhang, R. Cao, L. He, J. Wu, X. Li, Effects of triptolide on the pharmacokinetics of cyclophosphamide in rats: a possible role of cytochrome P3A4 inhibition, *Chin J Integr Med.* 20 (2014) 534–539. <https://doi.org/10.1007/s11655-014-1710-0>.
- [34] J.Y. Jao, W.J. Jusko, J.L. Cohen, Phenobarbital effects on cyclophosphamide pharmacokinetics in man, *Cancer Res.* 32 (1972) 2761–2764.
- [35] I. Burney, *Cancer Chemotherapy and Biotherapy*, Sultan Qaboos Univ Med J. 11 (2011) 424–425.
- [36] R.W.F. van Leeuwen, T. van Gelder, R.H.J. Mathijssen, F.G.A. Jansman, Drug-drug interactions with tyrosine-kinase inhibitors: a clinical perspective., *Lancet Oncol.* 15 (2014) e315–326. [https://doi.org/10.1016/S1470-2045\(13\)70579-5](https://doi.org/10.1016/S1470-2045(13)70579-5).
- [37] F.K. Engels, A.J. Ten Tije, S.D. Baker, C.K.K. Lee, W.J. Loos, A.G. Vulto, J. Verweij, A. Sparreboom, Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel, *Clin. Pharmacol. Ther.* 75 (2004) 448–454. <https://doi.org/10.1016/j.clpt.2004.01.001>.
- [38] P.A. Speth, Q.G. van Hoesel, C. Haanen, Clinical pharmacokinetics of doxorubicin, *Clin Pharmacokinet.* 15 (1988) 15–31. <https://doi.org/10.2165/00003088-198815010-00002>.
- [39] Z.P. Parra-Guillen, P.B. Berger, M. Haschke, M. Donzelli, D. Winogradova, B. Pfister, M. Früh, S. Gillessen, S. Krähenbühl, C. Kloft, M. Joerger, Role of Cytochrome P450 3A4 and 1A2 Phenotyping in Patients with Advanced Non-small-Cell Lung Cancer Receiving Erlotinib Treatment, *Basic Clin. Pharmacol. Toxicol.* 121 (2017) 309–315. <https://doi.org/10.1111/bcpt.12801>.
- [40] J.-H. Song, D.-X. Sun, B. Chen, D.-H. Ji, J. Pu, J. Xu, F.-D. Tian, L. Guo, Inhibition of CYP3A4 and CYP2C9 by podophyllotoxin: implication for clinical drug-drug interactions, *J. Biosci.* 36 (2011) 879–885.
- [41] K. Vishwanathan, P.A. Dickinson, K. So, K. Thomas, Y.-M. Chen, J. De Castro Carpeño, A.-M.C. Dingemans, H.R. Kim, J.-H. Kim, M.G. Krebs, J. Chih-Hsin Yang, K. Bui, D. Weilert, R.D. Harvey,

- The effect of itraconazole and rifampicin on the pharmacokinetics of osimertinib, *Br J Clin Pharmacol.* 84 (2018) 1156–1169. <https://doi.org/10.1111/bcp.13534>.
- [42] J.E. Desmarais, K.J. Looper, Interactions between tamoxifen and antidepressants via cytochrome P450 2D6, *J Clin Psychiatry.* 70 (2009) 1688–1697. <https://doi.org/10.4088/JCP.08r04856blu>.
- [43] M.P. Goetz, A. Kamal, M.M. Ames, Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response, *Clin. Pharmacol. Ther.* 83 (2008) 160–166. <https://doi.org/10.1038/sj.clpt.6100367>.
- [44] J.T. Ryman, B. Meibohm, Pharmacokinetics of Monoclonal Antibodies, *CPT Pharmacometrics Syst Pharmacol.* 6 (2017) 576–588. <https://doi.org/10.1002/psp4.12224>.
- [45] T. Katsila, A.P. Siskos, C. Tamvakopoulos, Peptide and protein drugs: the study of their metabolism and catabolism by mass spectrometry, *Mass Spectrom Rev.* 31 (2012) 110–133. <https://doi.org/10.1002/mas.20340>.
- [46] D.J. Handelsman, R.S. Swerdloff, Pharmacokinetics of Gonadotropin-Releasing Hormone and Its Analogs, *Endocr Rev.* 7 (1986) 95–105. <https://doi.org/10.1210/edrv-7-1-95>.
- [47] B.J. Gurley, S.F. Gardner, M.A. Hubbard, D.K. Williams, W.B. Gentry, I.A. Khan, A. Shah, In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes, *Clin. Pharmacol. Ther.* 77 (2005) 415–426. <https://doi.org/10.1016/j.clpt.2005.01.009>.
- [48] B. Gurley, M.A. Hubbard, D.K. Williams, J. Thaden, Y. Tong, W.B. Gentry, P. Breen, D.J. Carrier, S. Cheboyina, Assessing the clinical significance of botanical supplementation on human cytochrome P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin, *J Clin Pharmacol.* 46 (2006) 201–213. <https://doi.org/10.1177/0091270005284854>.
- [49] B.J. Gurley, A. Swain, M.A. Hubbard, D.K. Williams, G. Barone, F. Hartsfield, Y. Tong, D.J. Carrier, S. Cheboyina, S.K. Battu, Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: effects of milk thistle, black cohosh, goldenseal, kava kava, St. John's wort, and Echinacea, *Mol Nutr Food Res.* 52 (2008) 755–763. <https://doi.org/10.1002/mnfr.200600300>.
- [50] A.A. Albassam, M.-E.F. Mohamed, R.F. Frye, Inhibitory effect of six herbal extracts on CYP2C8 enzyme activity in human liver microsomes, *Xenobiotica.* 45 (2015) 406–412. <https://doi.org/10.3109/00498254.2014.989935>.
- [51] D.K. Sevier, J. Hokkanen, A. Tolonen, K. Abass, L. Tursas, O. Pelkonen, J.T. Ahokas, Rapid screening of commercially available herbal products for the inhibition of major human hepatic cytochrome P450 enzymes using the N-in-one cocktail, *Xenobiotica.* 40 (2010) 245–254. <https://doi.org/10.3109/00498251003592683>.
- [52] J.S. Markowitz, C.L. Devane, K.D. Chavin, R.M. Taylor, Y. Ruan, J.L. Donovan, Effects of garlic (*Allium sativum* L.) supplementation on cytochrome P450 2D6 and 3A4 activity in healthy volunteers, *Clin. Pharmacol. Ther.* 74 (2003) 170–177. [https://doi.org/10.1016/S0009-9236\(03\)00148-6](https://doi.org/10.1016/S0009-9236(03)00148-6).
- [53] B.J. Gurley, S.F. Gardner, M.A. Hubbard, D.K. Williams, W.B. Gentry, Y. Cui, C.Y.W. Ang, Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba, *Drugs Aging.* 22 (2005) 525–539.

- [54] B.J. Gurley, S.F. Gardner, M.A. Hubbard, D.K. Williams, W.B. Gentry, Y. Cui, C.Y.W. Ang, Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans, *Clin. Pharmacol. Ther.* 72 (2002) 276–287. <https://doi.org/10.1067/mcp.2002.126913>.
- [55] L.-J. Yang, L. Fan, Z.-Q. Liu, Y.-M. Mao, D. Guo, L.-H. Liu, Z.-R. Tan, L. Peng, C.-T. Han, D.-L. Hu, D. Wang, H.-H. Zhou, Effects of allicin on CYP2C19 and CYP3A4 activity in healthy volunteers with different CYP2C19 genotypes, *Eur. J. Clin. Pharmacol.* 65 (2009) 601–608. <https://doi.org/10.1007/s00228-008-0608-1>.
- [56] J. Hajda, K.M. Rentsch, C. Gubler, H. Steinert, B. Stieger, K. Fattinger, Garlic extract induces intestinal P-glycoprotein, but exhibits no effect on intestinal and hepatic CYP3A4 in humans, *Eur J Pharm Sci.* 41 (2010) 729–735. <https://doi.org/10.1016/j.ejps.2010.09.016>.
- [57] J.L. Donovan, K.D. Chavin, C.L. Devane, R.M. Taylor, J.-S. Wang, Y. Ruan, J.S. Markowitz, Green tea (*Camellia sinensis*) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers, *Drug Metab. Dispos.* 32 (2004) 906–908. <https://doi.org/10.1124/dmd.104.000083>.
- [58] H.-H.S. Chow, I.A. Hakim, D.R. Vining, J.A. Crowell, C.A. Cordova, W.M. Chew, M.-J. Xu, C.-H. Hsu, J. Ranger-Moore, D.S. Alberts, Effects of repeated green tea catechin administration on human cytochrome P450 activity, *Cancer Epidemiol. Biomarkers Prev.* 15 (2006) 2473–2476. <https://doi.org/10.1158/1055-9965.EPI-06-0365>.
- [59] S. Misaka, K. Kawabe, S. Onoue, J.P. Werba, M. Girolì, H. Watanabe, S. Yamada, Green tea extract affects the cytochrome P450 3A activity and pharmacokinetics of simvastatin in rats, *Drug Metab. Pharmacokinet.* 28 (2013) 514–518.
- [60] B. Edgar, D. Bailey, R. Bergstrand, G. Johnsson, C.G. Regårdh, Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine--and its potential clinical relevance, *Eur. J. Clin. Pharmacol.* 42 (1992) 313–317.
- [61] K.S. Lown, D.G. Bailey, R.J. Fontana, S.K. Janardan, C.H. Adair, L.A. Fortlage, M.B. Brown, W. Guo, P.B. Watkins, Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression, *J. Clin. Invest.* 99 (1997) 2545–2553. <https://doi.org/10.1172/JCI119439>.
- [62] J. Lundahl, C.G. Regårdh, B. Edgar, G. Johnsson, Effects of grapefruit juice ingestion--pharmacokinetics and haemodynamics of intravenously and orally administered felodipine in healthy men, *Eur. J. Clin. Pharmacol.* 52 (1997) 139–145.
- [63] J.J. Lilja, K.T. Kivistö, J.T. Backman, T.S. Lamberg, P.J. Neuvonen, Grapefruit juice substantially increases plasma concentrations of buspirone, *Clin. Pharmacol. Ther.* 64 (1998) 655–660. [https://doi.org/10.1016/S0009-9236\(98\)90056-X](https://doi.org/10.1016/S0009-9236(98)90056-X).
- [64] J.J. Lilja, K.T. Kivistö, P.J. Neuvonen, Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors, *Clin. Pharmacol. Ther.* 64 (1998) 477–483. [https://doi.org/10.1016/S0009-9236\(98\)90130-8](https://doi.org/10.1016/S0009-9236(98)90130-8).
- [65] P. Damkier, L.L. Hansen, K. Brosen, Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinidine, *Br J Clin Pharmacol.* 48 (1999) 829–838.
- [66] J.J. Lilja, K.T. Kivistö, J.T. Backman, P.J. Neuvonen, Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life, *Eur. J. Clin. Pharmacol.* 56 (2000) 411–415.

- [67] J.J. Lilja, K.T. Kivistö, P.J. Neuvonen, Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin, *Clin. Pharmacol. Ther.* 68 (2000) 384–390. <https://doi.org/10.1067/mcp.2000.110216>.
- [68] G.K. Dresser, D.G. Bailey, S.G. Carruthers, Grapefruit juice–felodipine interaction in the elderly, *Clin. Pharmacol. Ther.* 68 (2000) 28–34. <https://doi.org/10.1067/mcp.2000.107524>.
- [69] H. Takanaga, A. Ohnishi, H. Murakami, H. Matsuo, S. Higuchi, A. Urae, S. Irie, H. Furuie, K. Matsukuma, M. Kimura, K. Kawano, Y. Orii, T. Tanaka, Y. Sawada, Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects, *Clin. Pharmacol. Ther.* 67 (2000) 201–214. <https://doi.org/10.1067/mcp.2000.104215>.
- [70] M.P. Di Marco, D.J. Edwards, I.W. Wainer, M.P. Ducharme, The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein, *Life Sci.* 71 (2002) 1149–1160.
- [71] M.L. Veronese, L.P. Gillen, J.P. Burke, E.P. Dorval, W.W. Hauck, E. Pequignot, S.A. Waldman, H.E. Greenberg, Exposure-dependent inhibition of intestinal and hepatic CYP3A4 in vivo by grapefruit juice, *J Clin Pharmacol.* 43 (2003) 831–839.
- [72] D.J. Greenblatt, L.L. von Moltke, J.S. Harmatz, G. Chen, J.L. Weemhoff, C. Jen, C.J. Kelley, B.W. LeDuc, M.A. Zinny, Time course of recovery of cytochrome p450 3A function after single doses of grapefruit juice, *Clin. Pharmacol. Ther.* 74 (2003) 121–129. [https://doi.org/10.1016/S0009-9236\(03\)00118-8](https://doi.org/10.1016/S0009-9236(03)00118-8).
- [73] T.C. Goosen, D. Cillié, D.G. Bailey, C. Yu, K. He, P.F. Hollenberg, P.M. Woster, L. Cohen, J.A. Williams, M. Rheeders, H.P. Dijkstra, Bergamottin contribution to the grapefruit juice–felodipine interaction and disposition in humans, *Clin. Pharmacol. Ther.* 76 (2004) 607–617. <https://doi.org/10.1016/j.clpt.2004.08.019>.
- [74] J.J. Lilja, M. Neuvonen, P.J. Neuvonen, Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin, *Br J Clin Pharmacol.* 58 (2004) 56–60. <https://doi.org/10.1111/j.1365-2125.2004.02095.x>.
- [75] U.I. Schwarz, P.E. Johnston, D.G. Bailey, R.B. Kim, G. Mayo, A. Milstone, Impact of citrus soft drinks relative to grapefruit juice on ciclosporin disposition, *Br J Clin Pharmacol.* 62 (2006) 485–491. <https://doi.org/10.1111/j.1365-2125.2005.02519.x>.
- [76] D. Farkas, L.E. Oleson, Y. Zhao, J.S. Harmatz, M.A. Zinny, M.H. Court, D.J. Greenblatt, Pomegranate juice does not impair clearance of oral or intravenous midazolam, a probe for cytochrome P450-3A activity: comparison with grapefruit juice, *J Clin Pharmacol.* 47 (2007) 286–294. <https://doi.org/10.1177/0091270006298359>.
- [77] M.F. Paine, W.W. Widmer, S.N. Pusek, K.L. Beavers, A.B. Criss, J. Snyder, P.B. Watkins, Further characterization of a furanocoumarin-free grapefruit juice on drug disposition: studies with cyclosporine, *Am. J. Clin. Nutr.* 87 (2008) 863–871.
- [78] K. Strauch, U. Lutz, N. Bittner, W.K. Lutz, Dose-response relationship for the pharmacokinetic interaction of grapefruit juice with dextromethorphan investigated by human urinary metabolite profiles, *Food Chem. Toxicol.* 47 (2009) 1928–1935. <https://doi.org/10.1016/j.fct.2009.05.004>.
- [79] S. Tanaka, S. Uchida, S. Miyakawa, N. Inui, K. Takeuchi, H. Watanabe, N. Namiki, Comparison of inhibitory duration of grapefruit juice on organic anion-transporting polypeptide and cytochrome P450 3A4, *Biol. Pharm. Bull.* 36 (2013) 1936–1941.

- [80] S.-J. Park, C.-W. Yeo, E.-J. Shim, H. Kim, K.-H. Liu, J.-G. Shin, J.-H. Shon, Pomegranate juice does not affect the disposition of simvastatin in healthy subjects, *Eur J Drug Metab Pharmacokinet.* 41 (2016) 339–344. <https://doi.org/10.1007/s13318-015-0263-8>.
- [81] G.K. Dresser, B.L. Urquhart, J. Proniuk, A. Tieu, D.J. Freeman, J.M. Arnold, D.G. Bailey, Coffee inhibition of CYP3A4 in vitro was not translated to a grapefruit-like pharmacokinetic interaction clinically, *Pharmacol Res Perspect.* 5 (2017). <https://doi.org/10.1002/prp2.346>.
- [82] T.H. Nieminen, N.M. Hagelberg, T.I. Saari, M. Neuvonen, P.J. Neuvonen, K. Laine, K.T. Olkkola, Grapefruit juice enhances the exposure to oral oxycodone, *Basic Clin. Pharmacol. Toxicol.* 107 (2010) 782–788. <https://doi.org/10.1111/j.1742-7843.2010.00582.x>.
- [83] D.I. Min, Y.M. Ku, P.J. Perry, F.O. Ukah, K. Ashton, M.F. Martin, L.G. Hunsicker, Effect of grapefruit juice on cyclosporine pharmacokinetics in renal transplant patients, *Transplantation.* 62 (1996) 123–125.
- [84] M.P. Ducharme, R. Provenzano, M. Dehoorne-Smith, D.J. Edwards, Trough concentrations of cyclosporine in blood following administration with grapefruit juice, *Br J Clin Pharmacol.* 36 (1993) 457–459.
- [85] U. Fuhr, K. Klittich, A.H. Staib, Inhibitory effect of grapefruit juice and its bitter principal, naringenin, on CYP1A2 dependent metabolism of caffeine in man, *Br J Clin Pharmacol.* 35 (1993) 431–436.
- [86] U. Fuhr, A. Maier, A. Keller, V.W. Steinijans, R. Sauter, A.H. Staib, Lacking effect of grapefruit juice on theophylline pharmacokinetics, *Int J Clin Pharmacol Ther.* 33 (1995) 311–314.
- [87] H.Y. Lane, M.W. Jann, Y.C. Chang, C.C. Chiu, M.C. Huang, S.H. Lee, W.H. Chang, Repeated ingestion of grapefruit juice does not alter clozapine's steady-state plasma levels, effectiveness, and tolerability, *J Clin Psychiatry.* 62 (2001) 812–817.
- [88] S. Vandell, C. Netillard, M.C. Perault, A.M. Bel, Plasma levels of clozapine and desmethylozapine are unaffected by concomitant ingestion of grapefruit juice, *Eur. J. Clin. Pharmacol.* 56 (2000) 347–348.
- [89] Y. Xu, Y. Zhang, F. Zhou, Y. Zheng, X. Zhu, [Human pregnane X receptor-mediated transcriptional regulation of CYP3A4 by extracts of 7 traditional Chinese medicines], *Zhongguo Zhong Yao Za Zhi.* 36 (2011) 1524–1527.
- [90] Y.-F. Bi, H.-B. Zhu, J.-P. Xing, Z.-Q. Liu, F.-R. Song, [Effects of six kinds of Chinese herb extracts on the activities of rat liver microsomes in vitro], *Yao Xue Xue Bao.* 48 (2013) 1131–1135.
- [91] L.P. Volak, M.J. Hanley, G. Masse, S. Hazarika, J.S. Harmatz, V. Badmaev, M. Majeed, D.J. Greenblatt, M.H. Court, Effect of a herbal extract containing curcumin and piperine on midazolam, flurbiprofen and paracetamol (acetaminophen) pharmacokinetics in healthy volunteers, *Br J Clin Pharmacol.* 75 (2013) 450–462. <https://doi.org/10.1111/j.1365-2125.2012.04364.x>.
- [92] F.I. Al-Jenoobi, A.A. Al-Thukair, M.A. Alam, F.A. Abbas, A.M. Al-Mohizea, K.M. Alkharfy, S.A. Al-Suwayeh, Effect of *Curcuma longa* on CYP2D6- and CYP3A4-mediated metabolism of dextromethorphan in human liver microsomes and healthy human subjects, *Eur J Drug Metab Pharmacokinet.* 40 (2015) 61–66. <https://doi.org/10.1007/s13318-014-0180-2>.
- [93] M. Ikehata, N. Ohnishi, S. Egami, H. Kishi, Y. Shin, K. Takara, Y. Tsuchishita, N. Tokuda, S. Hori, Y. Yatani, Y. Fujimura, M. Kusumoto, R. Tatami, M. Yoshioka, K. Kuroda, S. Yamada, T. Yokoyama, Effects of turmeric extract on the pharmacokinetics of nifedipine after a single oral administration in healthy volunteers, *J Diet Suppl.* 5 (2008) 401–410. <https://doi.org/10.1080/19390210802519713>.

- [94] Y. Chen, W.-H. Liu, B.-L. Chen, L. Fan, Y. Han, G. Wang, D.-L. Hu, Z.-R. Tan, G. Zhou, S. Cao, H.-H. Zhou, Plant polyphenol curcumin significantly affects CYP1A2 and CYP2A6 activity in healthy, male Chinese volunteers, *Ann Pharmacother.* 44 (2010) 1038–1045.
<https://doi.org/10.1345/aph.1M533>.
- [95] D.-X. Sun, Z.-Z. Fang, Y.-Y. Zhang, Y.-F. Cao, L. Yang, J. Yin, Inhibitory Effects of Curcumenol on Human Liver Cytochrome P450 Enzymes, *Phytother. Res.* 24 (2010) 1213–1216.
<https://doi.org/10.1002/ptr.3102>.
- [96] S.R. Penzak, S.M. Robertson, J.D. Hunt, C. Chairez, C.Y. Malati, R.M. Alfaro, J.M. Stevenson, J.A. Kovacs, *Echinacea purpurea* significantly induces cytochrome P450 3A activity but does not alter lopinavir-ritonavir exposure in healthy subjects, *Pharmacotherapy.* 30 (2010) 797–805.
<https://doi.org/10.1592/phco.30.8.797>.
- [97] J.C. Gorski, S.-M. Huang, A. Pinto, M.A. Hamman, J.K. Hilligoss, N.A. Zaheer, M. Desai, M. Miller, S.D. Hall, The effect of echinacea (*Echinacea purpurea* root) on cytochrome P450 activity in vivo, *Clin. Pharmacol. Ther.* 75 (2004) 89–100.
<https://doi.org/10.1016/j.clpt.2003.09.013>.
- [98] B.J. Gurley, S.F. Gardner, M.A. Hubbard, D.K. Williams, W.B. Gentry, J. Carrier, I.A. Khan, D.J. Edwards, A. Shah, In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: *Citrus aurantium*, *Echinacea purpurea*, milk thistle, and saw palmetto, *Clin. Pharmacol. Ther.* 76 (2004) 428–440. <https://doi.org/10.1016/j.clpt.2004.07.007>.
- [99] Y.D. Muthiah, C.E. Ong, S.A. Sulaiman, R. Ismail, Inhibition of human cytochrome p450 2c8-catalyzed amodiaquine n-desethylation: Effect of five traditionally and commonly used herbs, *Pharmacogn. Res.* 8 (2016) 292–297.
- [100] W. Chatuphonprasert, K. Jarukamjorn, Impact of six fruits--banana, guava, mangosteen, pineapple, ripe mango and ripe papaya--on murine hepatic cytochrome P450 activities, *J Appl Toxicol.* 32 (2012) 994–1001. <https://doi.org/10.1002/jat.2740>.
- [101] R.S. Foti, J.T. Pearson, D.A. Rock, J.L. Wahlstrom, L.C. Wienkers, In vitro inhibition of multiple cytochrome P450 isoforms by xanthone derivatives from mangosteen extract, *Drug Metab. Dispos.* 37 (2009) 1848–1855. <https://doi.org/10.1124/dmd.109.028043>.
- [102] W. Sumsakul, W. Mahavorasirikul, K. Na-Bangchang, Inhibitory Activities of Thai Medicinal Plants with Promising Activities Against Malaria and Cholangiocarcinoma on Human Cytochrome P450, *Phytother Res.* 29 (2015) 1926–1933. <https://doi.org/10.1002/ptr.5485>.
- [103] P.O. Eck, P.A. Shah, P.V. Nerurkar, Modulation of cytochrome P450 1A2 and 3A4 by *Morinda citrifolia* (noni), *Euterpe oleracea* (acai), *Lycium barbarum* (goji) and *Garcinia mangostana* (mangosteen), *The FASEB Journal.* 23 (2009) 688.6–688.6.
https://doi.org/10.1096/fasebj.23.1_supplement.688.6.
- [104] G. Zadayan, D. Rokitta, S. Klement, A. Dienel, R. Hoerr, T. Gramatté, U. Fuhr, Effect of Ginkgo biloba special extract EGb 761® on human cytochrome P450 activity: a cocktail interaction study in healthy volunteers, *Eur. J. Clin. Pharmacol.* 68 (2012) 553–560.
<https://doi.org/10.1007/s00228-011-1174-5>.
- [105] G.A. Reed, J.M. Sunega, K.S. Peterson, C.-C. Stucky, D.K. Sullivan, J. Gray, M.S. Mayo, A. Hurwitz, Probe drug investigations suggest no pharmacokinetic interactions with ginseng and ginkgo biloba supplements, *The FASEB Journal.* 21 (2007) A1192–A1193.
<https://doi.org/10.1096/fasebj.21.6.A1192-d>.
- [106] H.-S. Kim, G.-Y. Kim, C.-W. Yeo, M. Oh, J.-L. Ghim, J.-H. Shon, E.-Y. Kim, D.-H. Kim, J.-G. Shin, The effect of Ginkgo biloba extracts on the pharmacokinetics and pharmacodynamics of

- cilostazol and its active metabolites in healthy Korean subjects, *Br J Clin Pharmacol.* 77 (2014) 821–830. <https://doi.org/10.1111/bcp.12236>.
- [107] S. Uchida, H. Yamada, X.D. Li, S. Maruyama, Y. Ohmori, T. Oki, H. Watanabe, K. Umegaki, K. Ohashi, S. Yamada, Effects of Ginkgo biloba extract on pharmacokinetics and pharmacodynamics of tolbutamide and midazolam in healthy volunteers, *J Clin Pharmacol.* 46 (2006) 1290–1298. <https://doi.org/10.1177/0091270006292628>.
- [108] J.S. Markowitz, J.L. Donovan, C. Lindsay DeVane, L. Sipkes, K.D. Chavin, Multiple-dose administration of Ginkgo biloba did not affect cytochrome P-450 2D6 or 3A4 activity in normal volunteers, *J Clin Psychopharmacol.* 23 (2003) 576–581. <https://doi.org/10.1097/01.jcp.0000095340.32154.c6>.
- [109] S.M. Robertson, R.T. Davey, J. Voell, E. Formentini, R.M. Alfaro, S.R. Penzak, Effect of Ginkgo biloba extract on lopinavir, midazolam and fexofenadine pharmacokinetics in healthy subjects, *Curr Med Res Opin.* 24 (2008) 591–599. <https://doi.org/10.1185/030079908X260871>.
- [110] A.S. Etheridge, S.R. Black, P.R. Patel, J. So, J.M. Mathews, 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.* 73 (2007) 731–741. <https://doi.org/10.1055/s-2007-981550>.
- [111] H.J. Chung, N.S. Kim, E.-J. Kim, T.K. Kim, K.H. Ryu, B.-Y. Lee, D.-H. Kim, C. Jin, H.H. Yoo, Negligible Effect of Ginkgo Biloba Extract on the Pharmacokinetics of Cilostazol, *Biomol. Ther.* 17 (2009) 311–317. <https://doi.org/10.4062/biomolther.2009.17.3.311>.
- [112] G.D. Anderson, G. Rosito, M.A. Mohustsy, G.W. Elmer, Drug interaction potential of soy extract and Panax ginseng, *J Clin Pharmacol.* 43 (2003) 643–648.
- [113] G. Wang, C.-Q. Xiao, Z. Li, D. Guo, Y. Chen, L. Fan, R.-H. Qian, X.-J. Peng, D.-L. Hu, H.-H. Zhou, Effect of soy extract administration on losartan pharmacokinetics in healthy female volunteers, *Ann Pharmacother.* 43 (2009) 1045–1049. <https://doi.org/10.1345/aph.1L690>.
- [114] C.-Q. Xiao, R. Chen, J. Lin, G. Wang, Y. Chen, Z.-R. Tan, H.-H. Zhou, Effect of genistein on the activities of cytochrome P450 3A and P-glycoprotein in Chinese healthy participants, *Xenobiotica.* 42 (2012) 173–178. <https://doi.org/10.3109/00498254.2011.615954>.
- [115] Y. Chen, C.-Q. Xiao, Y.-J. He, B.-L. Chen, G. Wang, G. Zhou, W. Zhang, Z.-R. Tan, S. Cao, L.-P. Wang, H.-H. Zhou, Genistein alters caffeine exposure in healthy female volunteers, *Eur. J. Clin. Pharmacol.* 67 (2011) 347–353. <https://doi.org/10.1007/s00228-010-0964-5>.
- [116] W.-X. Peng, H.-D. Li, H.-H. Zhou, Effect of daidzein on CYP1A2 activity and pharmacokinetics of theophylline in healthy volunteers, *Eur. J. Clin. Pharmacol.* 59 (2003) 237–241. <https://doi.org/10.1007/s00228-003-0596-0>.
- [117] M. Kopečna-Zapletalová, K. Krasulová, P. Anzenbacher, P. Hodek, E. Anzenbacherová, Interaction of isoflavonoids with human liver microsomal cytochromes P450: inhibition of CYP enzyme activities, *Xenobiotica.* 47 (2017) 324–331. <https://doi.org/10.1080/00498254.2016.1195028>.
- [118] S.U. Rehman, I.S. Kim, M.S. Choi, S.H. Kim, Y. Zhang, H.H. Yoo, Time-dependent Inhibition of CYP2C8 and CYP2C19 by Hedera helix Extracts, *A Traditional Respiratory Herbal Medicine, Molecules.* 22 (2017). <https://doi.org/10.3390/molecules22071241>.
- [119] B.J. Gurley, A. Swain, M.A. Hubbard, F. Hartsfield, J. Thaden, D.K. Williams, W.B. Gentry, Y. Tong, Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo, *Clin. Pharmacol. Ther.* 83 (2008) 61–69. <https://doi.org/10.1038/sj.clpt.6100222>.

- [120] H.-W. Xin, X.-C. Wu, Q. Li, A.-R. Yu, M.-Y. Zhong, Y.-Y. Liu, The effects of berberine on the pharmacokinetics of cyclosporin A in healthy volunteers, *Methods Find Exp Clin Pharmacol.* 28 (2006) 25–29. <https://doi.org/10.1358/mf.2006.28.1.962774>.
- [121] R.S. Sandhu, R.P. Prescilla, T.M. Simonelli, D.J. Edwards, Influence of goldenseal root on the pharmacokinetics of indinavir, *J Clin Pharmacol.* 43 (2003) 1283–1288. <https://doi.org/10.1177/0091270003258660>.
- [122] D. Dürr, B. Stieger, G.A. Kullak-Ublick, K.M. Rentsch, H.C. Steinert, P.J. Meier, K. Fattinger, St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4, *Clin. Pharmacol. Ther.* 68 (2000) 598–604. <https://doi.org/10.1067/mcp.2000.112240>.
- [123] C.A. Roby, G.D. Anderson, E. Kantor, D.A. Dryer, A.H. Burstein, St John's Wort: effect on CYP3A4 activity, *Clin. Pharmacol. Ther.* 67 (2000) 451–457. <https://doi.org/10.1067/mcp.2000.106793>.
- [124] S. Bauer, E. Störmer, R. Kerb, A. John, J. Brockmöller, I. Roots, Differential effects of Saint John's Wort (*hypericum perforatum*) on the urinary excretion of D-glucuronic acid and 6 β -hydroxycortisol in healthy volunteers, *Eur. J. Clin. Pharmacol.* 58 (2002) 581–585. <https://doi.org/10.1007/s00228-002-0527-5>.
- [125] G.K. Dresser, U.I. Schwarz, G.R. Wilkinson, R.B. Kim, Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects, *Clin. Pharmacol. Ther.* 73 (2003) 41–50. <https://doi.org/10.1067/mcp.2003.10>.
- [126] J.S. Markowitz, J.L. Donovan, C.L. DeVane, R.M. Taylor, Y. Ruan, J.-S. Wang, K.D. Chavin, Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme, *JAMA.* 290 (2003) 1500–1504. <https://doi.org/10.1001/jama.290.11.1500>.
- [127] L.-S. Wang, G. Zhou, B. Zhu, J. Wu, J.-G. Wang, A.M. Abd El-Aty, T. Li, J. Liu, T.-L. Yang, D. Wang, X.-Y. Zhong, H.-H. Zhou, St John's wort induces both cytochrome P450 3A4-catalyzed sulfoxidation and 2C19-dependent hydroxylation of omeprazole, *Clin. Pharmacol. Ther.* 75 (2004) 191–197. <https://doi.org/10.1016/j.clpt.2003.09.014>.
- [128] R. Xie, L.H. Tan, E.C. Polasek, C. Hong, M. Teillol-Foo, T. Gordi, A. Sharma, D.J. Nickens, T. Arakawa, D.W. Knuth, E.J. Antal, CYP3A and P-glycoprotein activity induction with St. John's Wort in healthy volunteers from 6 ethnic populations, *J Clin Pharmacol.* 45 (2005) 352–356. <https://doi.org/10.1177/0091270004273320>.
- [129] S.C. Mueller, J. Majcher-Peszynska, B. Uehleke, S. Klammt, R.G. Mundkowski, W. Miekisch, H. Sievers, S. Bauer, B. Frank, G. Kundt, B. Drewelow, The extent of induction of CYP3A by St. John's wort varies among products and is linked to hyperforin dose, *Eur. J. Clin. Pharmacol.* 62 (2006) 29–36. <https://doi.org/10.1007/s00228-005-0061-3>.
- [130] H. Imai, T. Kotegawa, K. Tsutsumi, T. Morimoto, N. Eshima, S. Nakano, K. Ohashi, The recovery time-course of CYP3A after induction by St John's wort administration, *Br J Clin Pharmacol.* 65 (2008) 701–707. <https://doi.org/10.1111/j.1365-2125.2008.03120.x>.
- [131] X.-D. Wang, J.-L. Li, Q.-B. Su, S. Guan, J. Chen, J. Du, Y.-W. He, J. Zeng, J.-X. Zhang, X. Chen, M. Huang, S.-F. Zhou, Impact of the haplotypes of the human pregnane X receptor gene on the basal and St John's wort-induced activity of cytochrome P450 3A4 enzyme, *Br J Clin Pharmacol.* 67 (2009) 255–261. <https://doi.org/10.1111/j.1365-2125.2008.03344.x>.
- [132] M.F. Hebert, J.M. Park, Y.-L. Chen, S. Akhtar, A.M. Larson, Effects of St. John's wort (*Hypericum perforatum*) on tacrolimus pharmacokinetics in healthy volunteers, *J Clin Pharmacol.* 44 (2004) 89–94. <https://doi.org/10.1177/0091270003261078>.

- [133] I. Mai, E. Störmer, S. Bauer, H. Krüger, K. Budde, I. Roots, Impact of St John's wort treatment on the pharmacokinetics of tacrolimus and mycophenolic acid in renal transplant patients, *Nephrol. Dial. Transplant.* 18 (2003) 819–822.
- [134] J.S. Markowitz, C.L. DeVane, D.W. Boulton, S.W. Carson, Z. Nahas, S.C. Risch, Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers, *Life Sci.* 66 (2000) PL133-139.
- [135] E.C. Bell, W.R. Ravis, H.M. Chan, Y.-J. Lin, Lack of pharmacokinetic interaction between St. John's wort and prednisone, *Ann Pharmacother.* 41 (2007) 1819–1824. <https://doi.org/10.1345/aph.1K316>.
- [136] T. Morimoto, T. Kotegawa, K. Tsutsumi, Y. Ohtani, H. Imai, S. Nakano, Effect of St. John's wort on the pharmacokinetics of theophylline in healthy volunteers, *J Clin Pharmacol.* 44 (2004) 95–101. <https://doi.org/10.1177/0091270003261496>.
- [137] M.W. Hruska, J.A. Cheong, T.Y. Langaee, R.F. Frye, Effect of St. John's wort administration on CYP2C8 mediated rosiglitazone metabolism., *Clin. Pharmacol. Ther.* 77 (2005) P35–P35. <https://doi.org/10.1016/j.clpt.2004.12.026>.
- [138] K.H. Liu, M.J. Kim, B.H. Jeon, J.H. Shon, I.J. Cha, K.H. Cho, S.S. Lee, J.G. Shin, Inhibition of human cytochrome P450 isoforms and NADPH-CYP reductase in vitro by 15 herbal medicines, including *Epimedium herba*, *J Clin Pharm Ther.* 31 (2006) 83–91. <https://doi.org/10.1111/j.1365-2710.2006.00706.x>.
- [139] C. Yu, X. Chai, L. Yu, S. Chen, S. Zeng, Identification of novel pregnane X receptor activators from traditional Chinese medicines, *J Ethnopharmacol.* 136 (2011) 137–143. <https://doi.org/10.1016/j.jep.2011.04.022>.
- [140] P.P. Maliakal, S. Wanwimolruk, Effect of herbal teas on hepatic drug metabolizing enzymes in rats, *J. Pharm. Pharmacol.* 53 (2001) 1323–1329.
- [141] R. Nowack, B. Nowak, Herbal teas interfere with cyclosporin levels in renal transplant patients, *Nephrol. Dial. Transplant.* 20 (2005) 2554–2556. <https://doi.org/10.1093/ndt/gfi003>.
- [142] M. Ganzera, P. Schneider, H. Stuppner, Inhibitory effects of the essential oil of chamomile (*Matricaria recutita* L.) and its major constituents on human cytochrome P450 enzymes, *Life Sci.* 78 (2006) 856–861. <https://doi.org/10.1016/j.lfs.2005.05.095>.
- [143] J.W. Budzinski, B.C. Foster, S. Vandenhoek, J.T. Arnason, An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures, *Phytomedicine.* 7 (2000) 273–282. [https://doi.org/10.1016/S0944-7113\(00\)80044-6](https://doi.org/10.1016/S0944-7113(00)80044-6).
- [144] G.K. Dresser, V. Wachter, S. Wong, H.T. Wong, D.G. Bailey, Evaluation of peppermint oil and ascorbyl palmitate as inhibitors of cytochrome P4503A4 activity in vitro and in vivo, *Clin. Pharmacol. Ther.* 72 (2002) 247–255. <https://doi.org/10.1067/mcp.2002.126409>.
- [145] A. Gelal, D. Balkan, D. Ozzeybek, Y.C. Kaplan, S. Gurler, H. Guven, N.L. Benowitz, Effect of menthol on the pharmacokinetics and pharmacodynamics of felodipine in healthy subjects, *Eur. J. Clin. Pharmacol.* 60 (2005) 785–790. <https://doi.org/10.1007/s00228-004-0847-8>.
- [146] M. Unger, A. Frank, 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.* 18 (2004) 2273–2281. <https://doi.org/10.1002/rcm.1621>.
- [147] E. Begas, A. Tsioutsouliti, E. Kouvaras, S.A. Haroutounian, K.M. Kasiotis, D. Kouretas, E. Asprodini, Effects of peppermint tea consumption on the activities of CYP1A2, CYP2A6,

- Xanthine Oxidase, N-acetyltransferase-2 and UDP-glucuronosyltransferases-1A1/1A6 in healthy volunteers, *Food Chem. Toxicol.* 100 (2017) 80–89. <https://doi.org/10.1016/j.fct.2016.12.021>.
- [148] A. Gelal, H. Guven, D. Balkan, L. Artok, N.L. Benowitz, Influence of menthol on caffeine disposition and pharmacodynamics in healthy female volunteers, *Eur. J. Clin. Pharmacol.* 59 (2003) 417–422. <https://doi.org/10.1007/s00228-003-0631-1>.
- [149] J. Chin, M. Mahfoudh, H. Abas, Interactions of *Orthosiphon stamineus* and *Morinda citrifolia* with hepatic aminopyrine metabolism by CYP3A in rats, (2010) 199–207.
- [150] C.Y. Malati, S.M. Robertson, J.D. Hunt, C. Chairez, R.M. Alfaro, J.A. Kovacs, S.R. Penzak, Influence of *Panax ginseng* on cytochrome P450 (CYP)3A and P-glycoprotein (P-gp) activity in healthy participants, *J Clin Pharmacol.* 52 (2012) 932–939. <https://doi.org/10.1177/0091270011407194>.
- [151] M.-G. Kim, Y. Kim, J.-Y. Jeon, D.-S. Kim, Effect of fermented red ginseng on cytochrome P450 and P-glycoprotein activity in healthy subjects, as evaluated using the cocktail approach, *Br J Clin Pharmacol.* 82 (2016) 1580–1590. <https://doi.org/10.1111/bcp.13080>.
- [152] Y.F. Zheng, S.H. Bae, E.J. Choi, J.B. Park, S.O. Kim, M.J. Jang, G.H. Park, W.G. Shin, E. Oh, S.K. Bae, Evaluation of the in vitro/in vivo drug interaction potential of BST204, a purified dry extract of ginseng, and its four bioactive ginsenosides through cytochrome P450 inhibition/induction and UDP-glucuronosyltransferase inhibition, *Food Chem. Toxicol.* 68 (2014) 117–127. <https://doi.org/10.1016/j.fct.2014.03.004>.
- [153] B.M. VandenBrink, R.S. Foti, D.A. Rock, L.C. Wienkers, J.L. Wahlstrom, Prediction of CYP2D6 drug interactions from in vitro data: evidence for substrate-dependent inhibition, *Drug Metab. Dispos.* 40 (2012) 47–53. <https://doi.org/10.1124/dmd.111.041210>.
- [154] J.S. Markowitz, J.L. Donovan, C.L. Devane, R.M. Taylor, Y. Ruan, J.-S. Wang, K.D. Chavin, Multiple doses of saw palmetto (*Serenoa repens*) did not alter cytochrome P450 2D6 and 3A4 activity in normal volunteers, *Clin. Pharmacol. Ther.* 74 (2003) 536–542. <https://doi.org/10.1016/j.clpt.2003.08.010>.
- [155] M. Kawaguchi-Suzuki, R.F. Frye, H.-J. Zhu, B.J. Brinda, K.D. Chavin, H.J. Bernstein, J.S. Markowitz, The effects of milk thistle (*Silybum marianum*) on human cytochrome P450 activity, *Drug Metab. Dispos.* 42 (2014) 1611–1616. <https://doi.org/10.1124/dmd.114.057232>.
- [156] U. Fuhr, S. Beckmann-Knopp, A. Jetter, H. Lück, U. Mengs, The effect of silymarin on oral nifedipine pharmacokinetics, *Planta Med.* 73 (2007) 1429–1435. <https://doi.org/10.1055/s-2007-990256>.
- [157] J. Doehmer, G. Weiss, G.P. McGregor, K. Appel, Assessment of a dry extract from milk thistle (*Silybum marianum*) for interference with human liver cytochrome-P450 activities, *Toxicol. Vitro.* 25 (2011) 21–27. <https://doi.org/10.1016/j.tiv.2010.09.001>.
- [158] A.A. Albassam, R.F. Frye, J.S. Markowitz, The effect of milk thistle (*Silybum marianum*) and its main flavonolignans on CYP2C8 enzyme activity in human liver microsomes, *Chem.-Biol. Interact.* 271 (2017) 24–29. <https://doi.org/10.1016/j.cbi.2017.04.025>.
- [159] J. Dusek, A. Carazo, F. Trejtnar, L. Hyrsova, O. Holas, T. Smutny, S. Micuda, P. Pavek, Steviol, an aglycone of steviol glycoside sweeteners, interacts with the pregnane X (PXR) and aryl hydrocarbon (AHR) receptors in detoxification regulation, *Food Chem. Toxicol.* 109 (2017) 130–142. <https://doi.org/10.1016/j.fct.2017.09.007>.
- [160] Y. Sato, T. Sasaki, S. Takahashi, T. Kumagai, K. Nagata, Development of a highly reproducible system to evaluate inhibition of cytochrome P450 3A4 activity by natural medicines, *J Pharm Pharm Sci.* 18 (2015) 316–327.

- [161] N. Ngo, Z. Yan, T.N. Graf, D.R. Carrizosa, A.D.M. Kashuba, E.C. Dees, N.H. Oberlies, M.F. Paine, Identification of a cranberry juice product that inhibits enteric CYP3A-mediated first-pass metabolism in humans, *Drug Metab. Dispos.* 37 (2009) 514–522. <https://doi.org/10.1124/dmd.108.024968>.
- [162] J. Grenier, C. Fradette, G. Morelli, G.J. Merritt, M. Vrandeć, M.P. Ducharme, Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans, *Clin. Pharmacol. Ther.* 79 (2006) 255–262. <https://doi.org/10.1016/j.clpt.2005.11.010>.
- [163] J.J. Lilja, J.T. Backman, P.J. Neuvonen, Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam—probes of CYP2C9, CYP1A2, and CYP3A4, *Clin. Pharmacol. Ther.* 81 (2007) 833–839. <https://doi.org/10.1038/sj.clpt.6100149>.
- [164] A.J. Langhammer, O.G. Nilsen, In vitro inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy, *Phytother Res.* 28 (2014) 603–610. <https://doi.org/10.1002/ptr.5037>.
- [165] J.L. Donovan, C.L. DeVane, K.D. Chavin, J.-S. Wang, B.B. Gibson, H.A. Gefroh, J.S. Markowitz, Multiple night-time doses of valerian (*Valeriana officinalis*) had minimal effects on CYP3A4 activity and no effect on CYP2D6 activity in healthy volunteers, *Drug Metab. Dispos.* 32 (2004) 1333–1336. <https://doi.org/10.1124/dmd.104.001164>.
- [166] M. Nishikawa, N. Ariyoshi, A. Kotani, I. Ishii, H. Nakamura, H. Nakasa, M. Ida, H. Nakamura, N. Kimura, M. Kimura, A. Hasegawa, F. Kusu, S. Ohmori, K. Nakazawa, M. Kitada, Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam, *Drug Metab. Pharmacokinet.* 19 (2004) 280–289.
- [167] S. Yang, S. Tsai, Hou, YC, Chao, PDL, Inductive modulation on P-glycoprotein and cytochrome 3A by resveratrol, a constituent of grapes, *Food Chemistry.* 133 (2012). <https://doi.org/10.1016/j.foodchem.2012.01.069>.
- [168] K.D. Mooiman, R.F. Maas-Bakker, J.J.M.A. Hendriks, P.C.D. Bank, H. Rosing, J.H. Beijnen, J.H.M. Schellens, I. Meijerman, 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.* 66 (2014) 865–874. <https://doi.org/10.1111/jphp.12208>.
- [169] C. Yu, Y.G. Shin, J.W. Kosmeder, J.M. Pezzuto, R.B. van Breemen, Liquid chromatography/tandem mass spectrometric determination of inhibition of human cytochrome P450 isozymes by resveratrol and resveratrol-3-sulfate, *Rapid Commun. Mass Spectrom.* 17 (2003) 307–313. <https://doi.org/10.1002/rcm.918>.
- [170] W.K. Chan, A.B. Delucchi, Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4, *Life Sci.* 67 (2000) 3103–3112.
- [171] B. Piver, F. Berthou, Y. Dreano, D. Lucas, Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non volatile red wine components, *Toxicol. Lett.* 125 (2001) 83–91.
- [172] H. Kim, Y.-J. Yoon, J.-H. Shon, I.-J. Cha, J.-G. Shin, K.-H. Liu, Inhibitory effects of fruit juices on CYP3A activity, *Drug Metab. Dispos.* 34 (2006) 521–523. <https://doi.org/10.1124/dmd.105.007930>.
- [173] S. Wanwimolruk, K. Wong, P. Wanwimolruk, Variable inhibitory effect of different brands of commercial herbal supplements on human cytochrome P-450 CYP3A4, *Drug Metabol Drug Interact.* 24 (2009) 17–35.
- [174] J.L. Raucy, Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products, *Drug Metab. Dispos.* 31 (2003) 533–539.

- [175] A.K.L. Goey, I. Meijerman, J.H. Beijnen, J.H.M. Schellens, The effect of grape seed extract on the pharmacokinetics of dextromethorphan in healthy volunteers, *Eur. J. Clin. Pharmacol.* 69 (2013) 1883–1890. <https://doi.org/10.1007/s00228-013-1558-9>.
- [176] S. Xiao Dong, Z. Zhi Ping, W. Zhong Xiao, C. Chong Shu, C. Fattore, G. Gatti, S. D'urso, E. Perucca, Possible enhancement of the first-pass metabolism of phenacetin by ingestion of grape juice in Chinese subjects, *Br J Clin Pharmacol.* 48 (1999) 638–640.
- [177] H.-M. Chiang, P.-D.L. Chao, S.-L. Hsiu, K.-C. Wen, S.-Y. Tsai, Y.-C. Hou, Ginger significantly decreased the oral bioavailability of cyclosporine in rats, *Am. J. Chin. Med.* 34 (2006) 845–855. <https://doi.org/10.1142/S0192415X06004338>.
- [178] K. Egashira, H. Sasaki, S. Higuchi, I. Ieiri, Food-drug interaction of tacrolimus with pomelo, ginger, and turmeric juice in rats, *Drug Metab. Pharmacokinet.* 27 (2012) 242–247.
- [179] T. Usia, T. Watabe, S. Kadota, Y. Tezuka, Mechanism-based inhibition of CYP3A4 by constituents of *Zingiber aromaticum*, *Biol. Pharm. Bull.* 28 (2005) 495–499.
- [180] null Subehan, T. Usia, S. Kadota, Y. Tezuka, Constituents of *Zingiber aromaticum* and their CYP3A4 and CYP2D6 inhibitory activity, *Chem. Pharm. Bull.* 53 (2005) 333–335.
- [181] Y. Kimura, H. Ito, T. Hatano, Effects of mace and nutmeg on human cytochrome P450 3A4 and 2C9 activity, *Biol. Pharm. Bull.* 33 (2010) 1977–1982.
- [182] J.-X. Qiu, Z.-W. Zhou, Z.-X. He, X. Zhang, S.-F. Zhou, S. Zhu, 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.* 9 (2015) 841–866. <https://doi.org/10.2147/DDDT.S74669>.
- [183] M. Li, P. Chen, Q. Yue, J. Li, R. Chu, W. Zhang, H. Wang, Pungent ginger components modulates human cytochrome P450 enzymes in vitro, *Acta Pharmacol. Sin.* 34 (2013) 1237–1242. <https://doi.org/10.1038/aps.2013.49>.
- [184] W. Zhang, L.-Y. Lim, Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism in vitro, *Drug Metab. Dispos.* 36 (2008) 1283–1290. <https://doi.org/10.1124/dmd.107.019737>.
- [185] H. Brandin, E. Viitanen, O. Myrberg, A.-K. Arvidsson, Effects of herbal medicinal products and food supplements on induction of CYP1A2, CYP3A4 and MDR1 in the human colon carcinoma cell line LS180, *Phytother Res.* 21 (2007) 239–244. <https://doi.org/10.1002/ptr.2057>.
- [186] I.S. Kim, S.Y. Kim, H.H. Yoo, Effects of an aqueous-ethanolic extract of ginger on cytochrome P450 enzyme-mediated drug metabolism, *Pharmazie.* 67 (2012) 1007–1009.
- [187] R. Mukkavilli, S.R. Gundala, C. Yang, S. Donthamsetty, G. Cantuaria, G.R. Jadhav, S. Vangala, M.D. Reid, R. Aneja, Modulation of cytochrome P450 metabolism and transport across intestinal epithelial barrier by ginger biophenolics, *PLoS ONE.* 9 (2014) e108386. <https://doi.org/10.1371/journal.pone.0108386>.
- [188] H.J. Kim, I.S. Kim, S.U. Rehman, S.K. Ha, K. Nakamura, H.H. Yoo, Effects of 6-paradol, an unsaturated ketone from gingers, on cytochrome P450-mediated drug metabolism, *Bioorg. Med. Chem. Lett.* 27 (2017) 1826–1830. <https://doi.org/10.1016/j.bmcl.2017.02.047>.
- [189] S. Pandit, P. Mukherjee, K. Mukherjee, R. Gajbhiye, Cytochrome P450 inhibitory potential of selected Indian spices—possible food drug interaction(Link), *Food Research International.* 45 (2012). <https://doi.org/10.1016/j.foodres.2011.08.021>.

- [190] T. Usia, H. Iwata, A. Hiratsuka, T. Watabe, S. Kadota, Y. Tezuka, CYP3A4 and CYP2D6 inhibitory activities of Indonesian medicinal plants, *Phytomedicine*. 13 (2006) 67–73. <https://doi.org/10.1016/j.phymed.2004.06.022>.
- [191] H.J. Kim, I.S. Kim, S.U. Rehman, S.K. Ha, K. Nakamura, H.H. Yoo, Effects of 6-paradol, an unsaturated ketone from gingers, on cytochrome P450-mediated drug metabolism, *Bioorg. Med. Chem. Lett.* 27 (2017) 1826–1830. <https://doi.org/10.1016/j.bmcl.2017.02.047>.
- [192] J. Ge, B.-X. Tan, Y. Chen, L. Yang, X.-C. Peng, H.-Z. Li, H.-J. Lin, Y. Zhao, M. Wei, K. Cheng, L.-H. Li, H. Dong, F. Gao, J.-P. He, Y. Wu, M. Qiu, Y.-L. Zhao, J.-M. Su, J.-M. Hou, J.-Y. Liu, Interaction of green tea polyphenol epigallocatechin-3-gallate with sunitinib: potential risk of diminished sunitinib bioavailability, *J. Mol. Med.* 89 (2011) 595–602. <https://doi.org/10.1007/s00109-011-0737-3>.
- [193] J. Qiao, C. Gu, W. Shang, J. Du, W. Yin, M. Zhu, W. Wang, M. Han, W. Lu, Effect of green tea on pharmacokinetics of 5-fluorouracil in rats and pharmacodynamics in human cell lines in vitro, *Food Chem. Toxicol.* 49 (2011) 1410–1415. <https://doi.org/10.1016/j.fct.2011.03.033>.
- [194] D. Park, J.H. Jeon, S. Shin, S.S. Joo, D.-H. Kang, S.-H. Moon, M.-J. Jang, Y.M. Cho, J.W. Kim, H.-J. Ji, B. Ahn, K.-W. Oh, Y.-B. Kim, Green tea extract increases cyclophosphamide-induced teratogenesis by modulating the expression of cytochrome P-450 mRNA, *Reprod. Toxicol.* 27 (2009) 79–84. <https://doi.org/10.1016/j.reprotox.2008.11.058>.
- [195] E.B. Golden, P.Y. Lam, A. Kardosh, K.J. Gaffney, E. Cadenas, S.G. Louie, N.A. Petasis, T.C. Chen, A.H. Schönthal, Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors, *Blood*. 113 (2009) 5927–5937. <https://doi.org/10.1182/blood-2008-07-171389>.
- [196] C.-K. Lee, S.-H. Ki, J.-S. Choi, Effects of oral curcumin on the pharmacokinetics of intravenous and oral etoposide in rats: possible role of intestinal CYP3A and P-gp inhibition by curcumin, *Biopharm Drug Dispos.* 32 (2011) 245–251. <https://doi.org/10.1002/bdd.754>.
- [197] FDA - Center for Drug Evaluation and Research, Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, (2020). https://downloads.regulations.gov/FDA-2017-D-5961-0023/attachment_1.pdf (accessed January 19, 2021).
- [198] W.P.D. Lemahieu, B.D. Maes, Y. Ghoo, P. Rutgeerts, K. Verbeke, Y. Vanrenterghem, Measurement of hepatic and intestinal CYP3A4 and PGP activity by combined po + iv [¹⁴C]erythromycin breath and urine test, *Am. J. Physiol. Gastrointest. Liver Physiol.* 285 (2003) G470–482. <https://doi.org/10.1152/ajpgi.00028.2003>.
- [199] M.P. Di Marco, D.J. Edwards, I.W. Wainer, M.P. Ducharme, The effect of grapefruit juice and seville orange juice on the pharmacokinetics of dextromethorphan: the role of gut CYP3A and P-glycoprotein, *Life Sci.* 71 (2002) 1149–1160.
- [200] D.G. Bailey, G.K. Dresser, J.R. Bend, Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice, *Clin. Pharmacol. Ther.* 73 (2003) 529–537. [https://doi.org/10.1016/S0009-9236\(03\)00051-1](https://doi.org/10.1016/S0009-9236(03)00051-1).
- [201] J.-H. Tu, D.-L. Hu, L.-L. Dai, Y. Sun, L. Fan, M. Zhang, Z.-R. Tan, Y. Chen, Z. Li, H.-H. Zhou, Effect of glycyrrhizin on CYP2C19 and CYP3A4 activity in healthy volunteers with different CYP2C19 genotypes, *Xenobiotica*. 40 (2010) 393–399. <https://doi.org/10.3109/00498251003748095>.
- [202] M.M. Rezaee, S. Kazemi, M.T. Kazemi, S. Gharooee, E. Yazdani, H. Gharooee, M.R. Shiran, A.A. Moghadamnia, The effect of piperine on midazolam plasma concentration in healthy

- volunteers, a research on the CYP3A-involving metabolism, *Daru*. 22 (2014) 8.
<https://doi.org/10.1186/2008-2231-22-8>.
- [203] S.K. Bedada, R. Appani, P.K. Boga, Effect of Piperine on the Metabolism and Pharmacokinetics of Carbamazepine in Healthy Volunteers, *Drug Res (Stuttg)*. 67 (2017) 46–51.
<https://doi.org/10.1055/s-0042-118173>.
- [204] J. Grenier, C. Fradette, G. Morelli, G.J. Merritt, M. Vrandeć, M.P. Ducharme, Pomelo juice, but not cranberry juice, affects the pharmacokinetics of cyclosporine in humans, *Clin. Pharmacol. Ther.* 79 (2006) 255–262. <https://doi.org/10.1016/j.clpt.2005.11.010>.
- [205] F.I. Al-Jenoobi, A.A. Al-Thukair, F.A. Abbas, M.J. Ansari, K.M. Alkharfy, A.M. Al-Mohizea, S.A. Al-Suwayeh, S. Jamil, Effect of black seed on dextromethorphan O- and N-demethylation in human liver microsomes and healthy human subjects., *Drug Metabolism Letters*. 4 (2010) 51–5.
- [206] H.-W. Xin, X.-C. Wu, Q. Li, A.-R. Yu, L. Xiong, Effects of Schisandra sphenanthera extract on the pharmacokinetics of midazolam in healthy volunteers, *Br. J. Clin. Pharmacol.* 67 (2009) 541–546. <https://doi.org/10.1111/j.1365-2125.2009.03383.x>.
- [207] W. Jiang, X. Wang, X. Xu, L. Kong, Effect of Schisandra sphenanthera extract on the concentration of tacrolimus in the blood of liver transplant patients, *Int. J. Clin. Pharmacol. Ther.* 48 (2010) 224–229.
- [208] E.J. Poulton, L. Levy, J.W. Lampe, D.D. Shen, J. Tracy, M.C. Shuhart, K.E. Thummel, D.L. Eaton, Sulforaphane is not an effective antagonist of the human pregnane X-receptor in vivo, *Toxicol. Appl. Pharmacol.* 266 (2013) 122–131. <https://doi.org/10.1016/j.taap.2012.10.029>.
- [209] K.-M. Duan, S.-Y. Wang, W. Ouyang, Y.-M. Mao, L.-J. Yang, Effect of quercetin on CYP3A activity in Chinese healthy participants, *J Clin Pharmacol.* 52 (2012) 940–946.
<https://doi.org/10.1177/0091270011406278>.
- [210] P. Bárány, P. Stenvinkel, A. Ottosson-Seeberger, A. Alvestrand, J. Morrow, J.J. Roberts, A.K. Salahudeen, Effect of 6 weeks of vitamin E administration on renal haemodynamic alterations following a single dose of neoral in healthy volunteers, *Nephrol. Dial. Transplant.* 16 (2001) 580–584.
- [211] H.-H.S. Chow, L.L. Garland, C.-H. Hsu, D.R. Vining, W.M. Chew, J.A. Miller, M. Perloff, J.A. Crowell, D.S. Alberts, Resveratrol Modulates Drug- and Carcinogen-Metabolizing Enzymes in a Healthy Volunteer Study, *Cancer Prev. Res.* 3 (2010) 1168–1175.
<https://doi.org/10.1158/1940-6207.CAPR-09-0155>.
- [212] S.K. Bedada, P. Nearati, Effect of resveratrol on the pharmacokinetics of carbamazepine in healthy human volunteers, *Phytother Res.* 29 (2015) 701–706.
<https://doi.org/10.1002/ptr.5302>.
- [213] J.H. Beijnen, J.H.M. Schellens, Drug interactions in oncology, *Lancet Oncol.* 5 (2004) 489–496.
[https://doi.org/10.1016/S1470-2045\(04\)01528-1](https://doi.org/10.1016/S1470-2045(04)01528-1).
- [214] P. Blower, R. de Wit, S. Goodin, M. Aapro, Drug-drug interactions in oncology: why are they important and can they be minimized?, *Crit. Rev. Oncol. Hematol.* 55 (2005) 117–142.
<https://doi.org/10.1016/j.critrevonc.2005.03.007>.
- [215] S. Parsad, M.J. Ratain, Drug-Drug Interactions With Oral Antineoplastic Agents, *JAMA Oncol.* 3 (2017) 736–738. <https://doi.org/10.1001/jamaoncol.2016.3323>.
- [216] Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement | The BMJ, (n.d.). <https://www.bmj.com/content/339/bmj.b2535> (accessed January 19, 2021).

- [217] A. Biber, H. Fischer, A. Römer, S.S. Chatterjee, Oral bioavailability of hyperforin from hypericum extracts in rats and human volunteers, *Pharmacopsychiatry*. 31 Suppl 1 (1998) 36–43. <https://doi.org/10.1055/s-2007-979344>.
- [218] D.J. Greenblatt, K.C. Patki, L.L. von Moltke, R.I. Shader, Drug interactions with grapefruit juice: an update, *J Clin Psychopharmacol*. 21 (2001) 357–359. <https://doi.org/10.1097/00004714-200108000-00001>.
- [219] K. Kobayashi, K. Urashima, N. Shimada, K. Chiba, Selectivities of human cytochrome P450 inhibitors toward rat P450 isoforms: study with cDNA-expressed systems of the rat, *Drug Metab. Dispos.* 31 (2003) 833–836. <https://doi.org/10.1124/dmd.31.7.833>.
- [220] M. Martignoni, G.M.M. Groothuis, R. de Kanter, Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction, *Expert Opin Drug Metab Toxicol*. 2 (2006) 875–894. <https://doi.org/10.1517/17425255.2.6.875>.
- [221] M.M. Iba, The effects of *Panax notoginseng* saponins (PNS) on the activities of “rat” CYP2C9, CYP2D6 and CYP3A4, *Phytother Res*. 28 (2014) 150–151. <https://doi.org/10.1002/ptr.5068>.
- [222] N. Shanks, R. Greek, J. Greek, Are animal models predictive for humans?, *Philos Ethics Humanit Med*. 4 (2009) 2. <https://doi.org/10.1186/1747-5341-4-2>.
- [223] C. Andrade, Potentially Significant Versus Clinically Significant Drug Interactions: Pomegranate Juice as a Case in Point, *J. Clin. Psychiatry*. 75 (2014) E292–E293. <https://doi.org/10.4088/JCP.14f09112>.
- [224] S. Misaka, R. Nakamura, S. Uchida, K. Takeuchi, N. Takahashi, N. Inui, K. Kosuge, S. Yamada, H. Watanabe, Effect of 2 Weeks’ Consumption of Pomegranate Juice on the Pharmacokinetics of a Single Dose of Midazolam: An Open-Label, Randomized, Single-Center, 2-Period Crossover Study in Healthy Japanese Volunteers, *Clinical Therapeutics*. 33 (2011) 246–252. <https://doi.org/10.1016/j.clinthera.2011.02.012>.
- [225] K.S. Abdlekawy, A.M. Donia, F. Elbarbry, Effects of Grapefruit and Pomegranate Juices on the Pharmacokinetic Properties of Dapoxetine and Midazolam in Healthy Subjects, *Eur. J. Drug Metabol. Pharmacokinet*. 42 (2017) 397–405. <https://doi.org/10.1007/s13318-016-0352-3>.
- [226] S.C. Nallani, T.A. Glauser, N. Hariparsad, K. Setchell, D.J. Buckley, A.R. Buckley, P.B. Desai, Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate, *Epilepsia*. 44 (2003) 1521–1528.
- [227] New Super-Potent Soy Extract | Life Extension, LifeExtension.Com. (n.d.). <https://www.lifeextension.com/Featured-Articles/Special/soyextrct/Page-01> (accessed November 30, 2018).
- [228] H.-H.S. Chow, L.L. Garland, C.-H. Hsu, D.R. Vining, W.M. Chew, J.A. Miller, M. Perloff, J.A. Crowell, D.S. Alberts, Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study, *Cancer Prev Res (Phila)*. 3 (2010) 1168–1175. <https://doi.org/10.1158/1940-6207.CAPR-09-0155>.
- [229] U. Stervbo, O. Vang, C. Bonnesen, A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine, *Food Chemistry*. 101 (2007) 449–457. <https://doi.org/10.1016/j.foodchem.2006.01.047>.
- [230] S. Weiskirchen, R. Weiskirchen, Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy?123, *Adv Nutr*. 7 (2016) 706–718. <https://doi.org/10.3945/an.115.011627>.
- [231] M.O. Magnusson, M.-L. Dahl, J. Cederberg, M.O. Karlsson, R. Sandström, Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe

- substrates midazolam, caffeine, and digoxin, *Clin. Pharmacol. Ther.* 84 (2008) 52–62. <https://doi.org/10.1038/sj.clpt.6100431>.
- [232] M. Zhu, S. Kaul, P. Nandy, D.M. Grasela, M. Pfister, Model-based approach to characterize efavirenz autoinduction and concurrent enzyme induction with carbamazepine, *Antimicrob. Agents Chemother.* 53 (2009) 2346–2353. <https://doi.org/10.1128/AAC.01120-08>.
- [233] J.C. Fleishaker, L.K. Pearson, G.R. Peters, Phenytoin causes a rapid increase in 6 beta-hydroxycortisol urinary excretion in humans—a putative measure of CYP3A induction, *J Pharm Sci.* 84 (1995) 292–294.
- [234] Tea Fact Sheet, (n.d.). <http://www.teausa.com/14655/tea-fact-sheet> (accessed December 10, 2019).
- [235] K.W. Lee, H.J. Lee, C.Y. Lee, Antioxidant Activity of Black Tea vs. Green Tea, *J Nutr.* 132 (2002) 785–785. <https://doi.org/10.1093/jn/132.4.785>.
- [236] K.A. Clauson, M.L. Santamarina, C.M. Buettner, J.S. Cauffield, Evaluation of presence of aspirin-related warnings with willow bark, *Ann Pharmacother.* 39 (2005) 1234–1237. <https://doi.org/10.1345/aph.1E650>.
- [237] C. Bunchorntavakul, K.R. Reddy, Review article: herbal and dietary supplement hepatotoxicity, *Aliment. Pharmacol. Ther.* 37 (2013) 3–17. <https://doi.org/10.1111/apt.12109>.
- [238] Y.S. de Boer, A.H. Sherker, Herbal and Dietary Supplement-Induced Liver Injury, *Clin Liver Dis.* 21 (2017) 135–149. <https://doi.org/10.1016/j.cld.2016.08.010>.
- [239] V.J. Navarro, I. Khan, E. Björnsson, L.B. Seeff, J. Serrano, J.H. Hoofnagle, Liver injury from herbal and dietary supplements, *Hepatology.* 65 (2017) 363–373. <https://doi.org/10.1002/hep.28813>.

Biography :

Paul Gougis is a clinical pharmacologist and an oncologist with several published works on drug-drug interactions and the pharmacology of targeted therapies.

Christian Funck-Brentano is professor of medicine and pharmacology and works on drug metabolism, drug-drug interactions and cardiac safety of cardiac and non-cardiac drugs.

Marc Hilmi is an oncologist with interest in clinical pharmacology and drug-drug interactions.

Arthur Geraud is a medical oncologist with several published works on target drug monitoring and pharmacology of targeted therapies

Olivier Mir is a medical oncologist with multiple works on the pharmacology of oral targeted therapies