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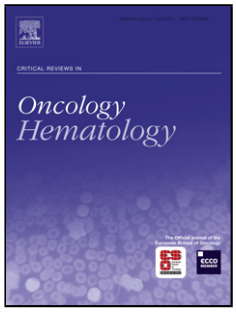

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Potential Cytochrome P450-mediated pharmacokinetic interactions between herbs, food, and dietary supplements and cancer treatments.

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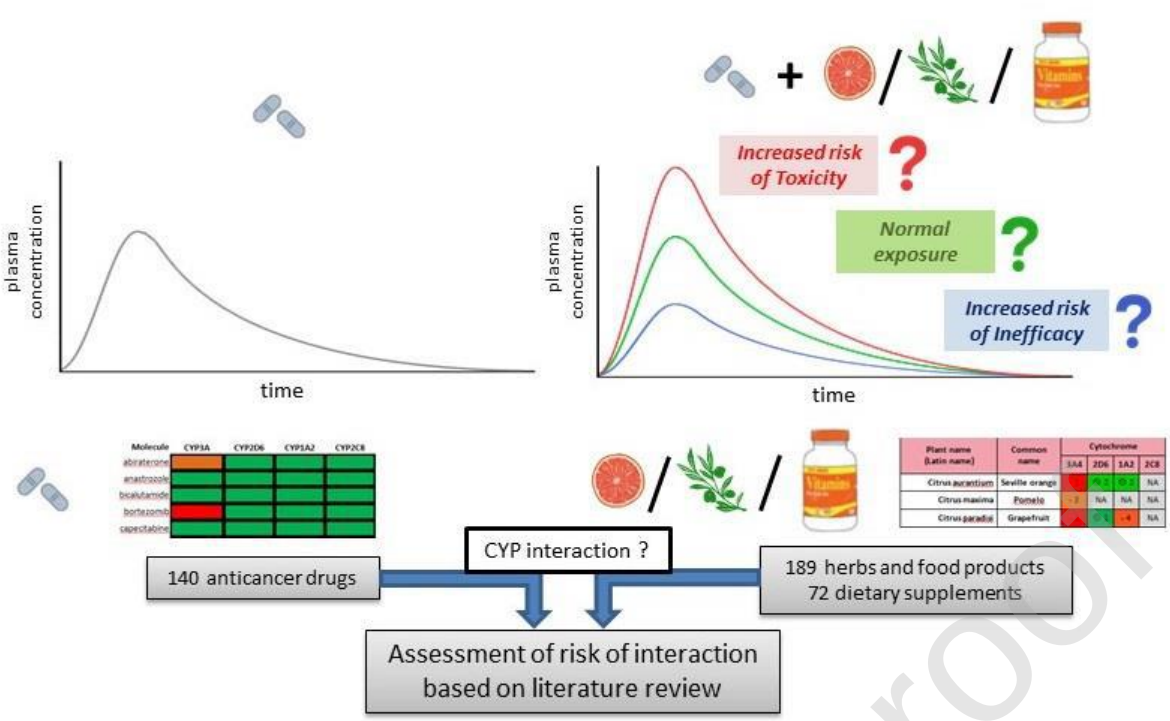
Graphical abstract



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 & *in vitro*) and none of them with an interaction
	⦸ 4	At least 3 *in vitro* 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 *in vitro* 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 *in vitro* 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 *in vitro* 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 *in vitro* 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 *in vitro* 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]

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

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
Cimicifuga racemosa	Black cohosh	Clin: NCS x2[47,48]	Clin: Mild inh x1[47] NCS x1[49]	Clin: NCS x1[47]	iVit : NS x2 [50,51]
Allium sativum	Garlic	Clin: NCS x5[20,52–56]	Clin: NCS x3[52–54]	Clin: NCS x2[53,54]	iVit : NS x1[50]
Camellia sinensis	Green tea*	Clin: NCS x1[57] inh x1[58]	Clin: NCS x2[57,58]	Clin: NCS x2[58]	iVit : inh x1[59]
Citrus paradisi	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
Crataegus monogyna	Hawthorn	iVit: ind x1[89] inh x1[90]	iVit : inh x1[90]	iVit : inh x1[90]	NA
Curcuma longa	Tumeric***	Clin✦: NCS x3[91–93]	Clin: inh x1[92]	Clin: inh x1[94]	iVit : NS (curcumenol)[95]
Desmodium adsendens	Desmodium	NA	NA	NA	NA
Echinacea purpurea	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]
Garcinia mangostana	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]
Ginkgo Biloba	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]
Glycine max	Soy	Clin : NCS x2 [112,113] ind genistein[114]	Clin: NCS x1[31]	Clin: inh genistein[115] / daidzein[116]	iVit: inh x1[117]
Hedera helix	English ivy	iVit : NS x1[118]	iVit: inh x1[118]	iVit : NS x1[118]	iVit: inh x1[118]
Hydrastis canadensis	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]
Hypericum perforatum	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]
Lepidium meyenii	Maca	NA	NA	NA	NA
Linum usitatissimum	Flaxseed	NA	NA	NA	NA
Lycium barbarum	Goji	iVit: inh x2[103,138] ind x1[139]	iVit: inh x1[138]	iVit: inh x1[103]	NA
Matricaria recutita	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
Marrubium vulgare	Horehound (white)	NA	NA	NA	NA
Mentha piperita	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
Morinda citrifolia	Noni	AM: inh x1[149] iVit: inh x2[6,103]	NA	iVit: inh[103]	NA
Panax ginseng	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]
Pausinystalia johimbe	Yohimbe	NA	iVit: inh x1[153]	NA	NA
Pelargonium sidoides	Umckaloabo	NA	NA	NA	NA
Piper methysticum	Kava kava	Clin: NCS x2[47,119]	Clin: NCS x2[47,49]	Clin: NCS x1[47]	NA
Prunus africana	Pygeum	NA	NA	NA	NA
Serenoa repens	Saw palmetto	Clin: NCS x2[98,154]	Clin: NCS x2[98,154]	Clin: NCS x1[98]	iVit : inh x1[50] NS x1[51]
Silybum marianum	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]
Stevia rebaudiana	Stevia	iVit: inh&ind (steviol)[159]	iVit: NS (steviol)[159]	iVit: ind (steviol)[159]	NA
Tanacetum parthenium	Feverfew	iVit: inh x2[146,160]	iVit: inh x1[146]	iVit: inh x1[146]	NA
Vaccinium macrocarpon	Cranberry	Clin: inh x1[161] NCS x2[162,163]	iVit: NS x1[164]	Clin: NCS x1[163]	iVit : inh x1[50]
Valeriana officinalis	Valerian	Clin: NCS x2[47,165]	Clin: NCS x2[47,165]	Clin: NCS x1[47]	iVit : NS x2[50,51]
Vitis vinifera	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]
Zingiber officinale	Ginger	AM: [177,178]° 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)

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
Acmella oleracea	Spilanthes	NA	NA	NA	NA
Aesculus hippocastanum	Horse chestnut	- 4	- 5	+/- p	NA
Agaricus subrufescens	Agaricus	- 5	NA	NA	NA
Aloe Vera	Aloe	- 4	- 5	NA	NA
Allium sativum	Garlic	⃠ 1	⃠ 1	⃠ 1	⃠ 5
Andrographis paniculata	Andrographis	- 5	⃠ 5	- 5	NA
Angelica sinensis	Dong quai	+ 5	+ 5	+/- p	NA
Annona muricata	Soursop	- 5	- 5	⃠ 5	NA
Arctium lappa	Burdock	- 5	NA	NA	NA
Arnica montana	Arnica	NA	NA	NA	NA
Artemisia annua	Sweet wormwood	- 5	NA	NA	NA
Arthrospira platensis	Spirulina	⃠ 5	NA	- 5	NA
Asimina triloba	Pawpaw	NA	NA	NA	NA
Aspalathus linearis	Rooibos	- 5	NA	NA	- 5
Asparagus cochinchinensis	Tian men dong	NA	NA	NA	NA
Astragalus membranaceus	Astragalus	+/- p	⃠ 5	- 5	NA
Averrhoa carambola	Star fruit (Carambola)	- 4	NA	NA	NA
Azadirachta indica	Neem	NA	NA	NA	NA
Borago officinalis	Borage	NA	NA	NA	NA
Boswellia serrata	Indian olibanum	NA	NA	NA	NA
Brassica oleracea	**Broccoli sprouts extracts / kale**	- 3	- 5	- 5	NA
Bupleurum falcatum (chinense)	Thoroughwax	+/- p	+ 5	⃠ 3	NA
Calendula officinalis	Calendula	NA	NA	NA	NA
Camellia sinensis	**Green tea**	- 3	⃠ 1	⃠ 2	- 5
Cannabis sativa	Cannabis	⃠ 2	NA	- 4	NA
Carica papaya	Papaya	⃠ 5	NA	⃠ 5	NA
Cassia angustifolia	Senna (Alexandrina)	NA	NA	NA	NA
Centella asiatica	Gotu kola	- 5	- 5	⃠ 4	NA
Cimicifuga racemosa	Black cohosh	⃠ 1	- 3	⃠ 2	⃠ 5
Citrus aurantifolia	**Lime**	- 3	NA	NA	NA
Citrus aurantium	**Seville orange**	- 1	⃠ 2	⃠ 2	NA
Citrus maxima	**Pomelo**	- 3	NA	NA	NA
Citrus paradisi	**Grapefruit**	- 1	⃠ 1	- 4	NA
Chamaemelum nobile	Camomile (roman chamomile)	⃠ 5	⃠ 5	- 5	NA
Chrysanthemum indicum	Indian Chrysanthe-mum	⃠ 5	NA	NA	NA
Chrysanthemum morifolium	Chrysanthe-mum	⃠ 5	NA	NA	NA
Cinnamomum verum/cassia	Cinnamon	- 5	NA	NA	NA
Cinnamomum camphora	Camphor	NA	NA	NA	NA
Cnicus benedictus	Blessed thistle	NA	NA	NA	NA
Commiphora myrrha	Myrrh	+ 5	NA	+ 5	NA
Commiphora wightii	Guggul	+ 5	NA	NA	NA
Convolvulis arvensis	Bindweed	NA	NA	NA	NA
Coptis chinensis	Huanglian	+ 5	- 5	⃠ 5	⃠ 5
Croton lechleri	Sangre de drago	NA	NA	NA	NA
Crataegus monogyna	Hawthorn	+/- p	- 5	- 5	NA
Curcuma longa	Tumeric	⃠ 1	- 2	- 2	⃠ 5
Cymbopogon citratus	Lemongrass	NA	NA	NA	NA
Dendranthema boreale	Chrysanthe-mum boreale	NA	NA	NA	NA
Desmodium adsendens	Desmodium	NA	NA	NA	NA
Dioscorea alata	Purple yam	NA	NA	NA	NA
oscorea villosa	Wild yam	- 5	NA	NA	NA
Echinacea purpurea	**Echinacea**	+ 1	⃠ 1	- 2	⃠ 5
Eleutherococcus senticosus	Siberian Ginseng	⃠ 2	⃠ 2	NA	NA
Ephedra sinica	Ephedra	⃠ 2	NA	⃠ 2	NA
Epimedium sagittatum	Epimedium	NA	NA	NA	NA

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

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

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

Plant name (Latin name)	**Common name**	**Cytochrome**			
		3A4	**2D6**	**1A2**	**2C8**
Trigonella foenum-graecum	Fenugreek	⦸ 2	⦸ 2	NA	NA
Triticum aestivum	Wheat grass	NA	NA	NA	NA
Turnera diffusa	Damiana	NA	NA	NA	NA
Ulmus rubra	Slippery elm	NA	NA	NA	NA
Uncaria tomentosa	Cat's claw	- 4	NA	NA	NA
Urtica dioica	Nettle	- 5	NA	NA	NA
Vaccinium corymbosum	Blueberry (American)	⦸ 2	NA	NA	NA
Vaccinium macrocarpon	**Cranberry**	- 2	⦸ 5	⦸ 2	- 5
Vaccinium myrtillus	Bilberry	NA	NA	NA	NA
Valeriana officinalis	Valerian	⦸ 1	⦸ 1	⦸ 2	⦸ 5
Viscum album	Mistletoe	- 5	NA	NA	NA
Vitis vinifera	Grape	- 4	⦸ 2	+ 2	- 5
Vitex agnus-castus	Chasteberry	- 5	- 5	- 5	NA
Withania somnifera	Ashwagandha	- 5	⦸ 5	⦸ 5	NA
Zingiber officinale	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
Capsaïcin	+/- p	⦸ 5	- 5	NA
Cesium chloride	NA	NA	NA	NA
Chitosan / Deacetylated chitin	- 4	NA	NA	NA
Chondroïtine	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
Protocel	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
Açai	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 (*Citrus paradisi*) [60–78,24,79,23,80–84]	Saint-John's wort (*Hypericum perforatum*) [29,30,53,54,122–133]	
	Sevilla orange (*Citrus aurantium*) [198,199]		
	Goldenseal (*Hydrastis canadensis*) [47,119,120]		
mild interaction	Lime (*Citrus arantifolia*) [200]	Ginseng (*Panax ginseng*) [150]	Ginkgo (*Ginkgo biloba*) [107,109]
	Cranberry (*Vaccinium macrocarpon*) [161]	Licorice (*Glycyrrhiza glabra*) [201]	Piperine / pepper extracts (*Piper nigrum*) [202,203]
	Green tea (*Camellia sinensis*) [58]	Echinacea (*Echinacea purpurea*) [96,97]	
	Peppermint (*Mentha piperita*) [144]	Soy extracts (*Glycine max*) / genistein [114]	
	Pomelo (*Citrus maxima*) [204]		
	Black seed (*Nigella sativa*) [205]		
	Wuzhi (*Schisandra sphenanthera*) [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 Cmax/IC50 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 Green tea

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.

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Biography :

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