Herb–Drug Interactions in Oncology: Focus on Mechanisms of Induction

IRMA MEIJERMAN, a JOS H. BEIJNEN, a,b JAN H.M. SCHELLENS a,c

aBiomedical Analysis, Department of Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands; bDepartment of Pharmacy & Pharmacology, Slotervaart Hospital, Amsterdam, The Netherlands; cDepartment of Medical Oncology & Experimental Therapy, Antoni van Leeuwenhoek Hospital/The Netherlands Cancer Institute, Amsterdam, The Netherlands

Key Words. Herb–drug interactions • Chemotherapeutics • Induction • PXR • VDR • CAR

ABSTRACT

An increasing number of cancer patients are using complementary and alternative medicines (CAM) in combination with their conventional chemotherapeutic treatment. Considering the narrow therapeutic window of oncolytic drugs, this CAM use increases the risk of clinically relevant herb–anticancer drug interactions. Such a relevant interaction is that of St. John’s wort with the anticancer drugs irinotecan and imatinib. It is, however, estimated that CAM–anticancer drug interactions are responsible for substantially more unexpected toxicities of chemotherapeutic drugs and possible undertreatment seen in cancer patients.

Induction of drug-metabolizing enzymes and ATP-binding cassette drug transporters can be one of the mechanisms behind CAM–anticancer drug interactions. Induction will often lead to therapeutic failure because of lower plasma levels of the anticancer drugs, and will easily go unrecognized in cancer treatment, where therapeutic failure is common.

Recently identified nuclear receptors, such as the pregnane X receptor, the constitutive androstane receptor, and the vitamin D-binding receptor, play an important role in the induction of metabolizing enzymes and drug transporters. This knowledge has already been an aid in the identification of some CAM probably capable of causing interactions with anticancer drugs: kava-kava, vitamin E, quercetin, ginseng, garlic, β-carotene, and echinacea. Evidently, more research is necessary to prevent therapeutic failure and toxicity in cancer patients and to establish guidelines for CAM use. The Oncologist 2006;11:742–752
**Introducation**

The use of complementary and alternative medicines (CAM) by cancer patients in the Western world has grown rapidly. Importantly, although many cancer patients are using CAM in combination with their conventional therapy, more than 72% of them do not inform their treating physician about CAM use [1].

With the use of CAM in combination with conventional chemotherapeutics, there is an increasing risk for unwanted interactions, especially because of the narrow therapeutic index of most oncolytic drugs. Although, as a result of a lack of investigations, reports about clinically relevant pharmacokinetic (PK) interactions of CAM with chemotherapeutic drugs are scarce, it is expected that CAM–anticancer drug interactions contribute significantly to the interindividual variations in PK and clinical problems of unexpected toxicities and undertreatment seen in cancer patients. McCune et al. [2] estimated that, of the population of patients taking chemotherapeutic drugs and CAM, at least 27% were at risk for developing clinically relevant CAM–drug interactions. It is therefore of utmost importance that treating oncologists are aware of the possibility and consequences of CAM–drug interactions. This review provides more information about currently known, clinically relevant PK CAM–drug interactions in oncology, with a focus on the mechanisms and clinical implications of enzyme induction. The accompanying article by Tascilar et al. [3] in this issue of *The Oncologist* describes overall clinical implications of CAM use by cancer patients.

**Clinically Relevant CAM–Anticancer Drug Interactions**

One of the best known examples of a clinically significant effect of CAM on the PK of chemotherapeutic drugs is the herbal product St. John’s wort (SJW). SJW is very popular among cancer patients because of its supposed activity in mild to moderate forms of depression [4]. In cancer patients using SJW in combination with irinotecan, the plasma levels of SN-38, the active metabolite of irinotecan, were 42% lower [4]. The same effect was observed in rats, in which long-term (14 days) exposure to SJW resulted in a significantly lower maximum observed concentration (C\text{max}) of both irinotecan and SN-38 [5]. In cancer patients, the degree of myelosuppression was substantially worse in the absence of SJW [4]. Similarly, in the rat, gastrointestinal and hematological toxicities after irinotecan injection were alleviated in the presence of SJW [5]. Because of the extensive reduction in the plasma levels of SN-38, patients should be advised to refrain from SJW use to prevent undertreatment (Fig. 1) [4]. The same advice could be given to patients that are going to be treated with the protein-tyrosine kinase inhibitor imatinib. Healthy subjects taking imatinib combined with SJW showed a 43% greater imatinib clearance, with up to 32% lower mean area under the concentration–time curve (AUC) and significantly lower C\text{max} and half-life (t\text{1/2}) [6, 7]. Although this may appear as a modest effect, it could result in plasma concentrations of imatinib below the minimum effective concentration after taking the standard 400-mg dose. In the case of imatinib, however, one remark has to be made. The main metabolite formed after metabolism of imatinib, an N-desmethylated piperazine derivative, has been shown to have in vitro antitumor activity comparable with that of imatinib [6, 7]. After SJW intake, the C\text{max} of this metabolite was slightly greater, although the AUC from 0–72 hours was not different. The real clinical effect of the lower imatinib plasma levels after SJW intake is therefore unclear and has to be further investigated.

Based on in vitro data obtained in human hepatocyte cultures, a greater docetaxel metabolism can also be expected in patients using SJW chronically [8].

Another example of the effect of CAM on the PK of anticancer drugs is grapefruit juice. Grapefruit juice intake resulted in a 26.2% lower AUC of etoposide after oral intake. The median absolute bioavailabilities with and without pretreatment with grapefruit juice were 52.4% and 73.2%, respectively [9].

Although to our knowledge no other clinically relevant interactions of CAM with the PK of chemotherapeutic drugs in patients have been reported so far, these examples are convincing enough to assume that CAM–anticancer drug interactions can be responsible for significantly more of the large interindividual variations in the response to chemotherapeutic treatment seen in the clinic. This assumption is supported by several in vitro and in vivo studies, and by clinical studies with other drugs, that show that some CAMs probably have the capacity to influence plasma levels of chemotherapeutic drugs [10–14].

**Mechanisms of CAM–Anticancer Drug Interactions**

CAM–anticancer drug interactions can occur at the pharmacological, pharmacodynamic, or PK level [15]. Interactions at the PK level are the most likely interactions to occur and involve changes in absorption, distribution, metabolism, or excretion of the chemotherapeutic drug. Almost all PK interactions at the level of metabolism of chemotherapeutic drugs involve cytochrome P450 (CYP) metabolizing enzymes or phase II enzymes, especially uridine diphosphoglucuronosyl transferase (UGT). Of the CYP enzymes, CYP3A4 is the most important enzyme in the metabolism of anticancer drugs (Table 1). In addition, many anticancer drugs are substrates for the ATP-binding
The cassette (ABC) family of drug transporters like P-glycoprotein (Pgp, ABCB-1), breast cancer resistance protein (BCRP, ABCG-2), multidrug resistance associated protein 1 (MRP-1, ABCC-1), and MRP-2 (ABCC-2) (Table 2). These transporters are involved in the oral bioavailability and hepatobiliary, direct intestinal, and urinary excretion of chemotherapeutics and their metabolites (Table 2) [16–18]. Increased expression of transporters is also one of the pathways responsible for multidrug resistance of cancer cells [18].

PK interactions between CAM and oncolytic drugs occur when CAM, or the active constituents of CAM, inhibit or induce the metabolizing enzymes or drug transporters involved in the PK disposition of chemotherapeutic drugs (Tables 1, 2). Inhibition occurs when CAM are able to decrease the normal activity level of a metabolic enzyme or drug transporter via a competitive or noncompetitive mechanism. Induction is a much slower process, in which CAM increase the mRNA and protein levels of the relevant metabolizing enzyme or drug transporter. This process is reversible, and enzyme levels are reduced to normal if CAM use is discontinued. CAM-induced PK changes can lead to significant clinical effects in cancer patients, like a lower therapeutic efficacy or greater toxicity of the chemotherapeutic drug [15, 19]. In the example of SJW and irinotecan or imatinib, induction of the enzymes involved in the metabolism and transport of these chemotherapeutic drugs is responsible for the lower plasma levels. SJW has been shown to induce both CYP3A4 as well as Pgp in vitro and in vivo [20–22] and CYP2C19 in healthy subjects [8]. From the other clinically relevant interaction, grapefruit juice with etoposide, it is known that grapefruit juice is a potent inhibitor of intestinal CYP3A4. Based on this fact, a greater AUC of the CYP3A4 substrate etoposide would have been expected after oral intake of the drug combined with grapefruit juice. However, in the patients studied, a lower AUC of etoposide was observed. The explanation given by the authors for this lower AUC was a possible inductive effect of grapefruit juice on Pgp-mediated transport of etoposide [9].

In general, CYP inhibition will lead to higher levels of the cytotoxic drug, causing recognizable, greater toxicity, unless the cytotoxic drug is an inactive prodrug such as

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**Figure 1.** The effect of hyperforin on irinotecan therapy. Hyperforin, the active constituent of St. John’s wort, binds to and activates the pregnane X receptor (PXR). Upon activation, PXR forms a heterodimer with the 9-cis retinoic acid receptor (RXR), and this complex binds to the xenobiotic response elements (PXRE) in the cytochrome P450 3A4 (CYP3A4) gene. The transcription of the gene is increased, and more CYP3A4 is formed, thereby increasing the metabolism of irinotecan into an inactive metabolite, oxidized irinotecan. The amount of irinotecan left to be metabolized into SN-38 decreases, leaving less active SN-38 and a lower therapeutic efficacy of irinotecan.
cyclophosphamide or ifosfamide. For detailed information about CAM–drug interactions resulting from inhibition, the reader is referred to some recent reviews [10–14, 23]. Summarized, CAMs that have already been shown to actively inhibit CYP enzymes are: garlic [23], constituents of Ginkgo biloba [23, 24], kava [23], ginseng [25], Echinacea purpurea [24], milk thistle (silybin) [26–28], and evening primrose oil (cis-linoleic acid) [23]. Pgp activity was shown to be inhibited by curcumin, ginsenosides, piperine, some catechins from green tea, quercetin, and silymarin [14, 29, 30]. Genistein is a substrate of BCRP and therefore acts as a competitive inhibitor of BCRP-mediated transport [31].

Induction of CYP or drug transporters will, in the case of active parent drugs, often lead to therapeutic failure because of lower plasma levels of the chemotherapeutic drug. As therapeutic failure in the treatment of cancer

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Table 1. Metabolizing enzymes involved in the metabolism of chemotherapeutic drugs [15, 85–87]

<table>
<thead>
<tr>
<th>Metabolizing enzyme</th>
<th>Chemotherapeutic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1, CYP1A2</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Cyclophosphamide, ifosfamide, tegafur</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Cyclophosphamide, ifosfamide</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Cyclophosphamide, ifosfamide, paclitaxel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Cyclophosphamide, ifosfamide</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Teniposide</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Tamoxifen, doxorubicin, vinblastine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Etoposide, tipifarnib</td>
</tr>
</tbody>
</table>

Phase II enzymes

- N-acetyltransferase 2: Amonafide
- Glutathion S-transferase: Busulfan, etoposide, doxorubicin, carboplatin, cisplatin, cyclophosphamide, thiotepa
- Sulfotransferases: Tamoxifen, mitomycin C
- Thiopurine methyltransferase: 6-Mercaptopurine, 6-thioguanine
- Uridine diphosphate glucuronosyltransferase: Irinotecan, epirubicin, topotecan, etoposide, flavopiridol, tipifarnib

Other

- Carboxylesterase CES2: Irinotecan
- Dihydropyrimidine dehydrogenase: 5-Fluorouracil, capecitabine

Table 2. ATP-binding cassette drug transporters involved in the transport of chemotherapeutic drugs [17, 18, 86]

<table>
<thead>
<tr>
<th>Drug transporter</th>
<th>Chemotherapeutic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein (ABCB-1, MDR-1)</td>
<td>Actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, eripubicin, bisantrene</td>
</tr>
<tr>
<td>MRP-1 (ABCC-1)</td>
<td>Etoposide, teniposide, vincristine, vinblastine, doxorubicin, daunorubicin, epirubicin, idarubicin, topotecan, irinotecan, mitoxantrone, chlorambucil, methotrexate, melphalan</td>
</tr>
<tr>
<td>MRP-2 (ABCC-2)</td>
<td>SN-38G (irinotecan metabolite), methotrexate, sulfonpyrazone, vinblastine</td>
</tr>
<tr>
<td>BCRP (ABCG-2, MXR)</td>
<td>9-Aminocamptothecin, daunorubicin, epirubicin, etoposide, lurtotecan, mitoxantrone, SN-38 (irinotecan metabolite), topotecan</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; MDR, multidrug resistance gene; MRP, multidrug resistance-associated protein; MXR, mitoxantrone resistance-associated protein.
is common, very often this effect may not be recognized as the consequence of an interaction with CAM. Only just recently, the mechanisms behind induction of metabolizing enzymes and drug transporters were discovered, and this knowledge has led to new possibilities for the identification of CAM capable of causing induction. So, although CAM–drug interaction based on inhibition processes can be of clinical importance in oncology, this review further focuses on how the mechanistic knowledge about induction processes can be an aid in the prediction of clinically relevant CAM–anticancer drug interactions. It also gives an overview of the current knowledge about the induction capacity of CAM. Ultimately, more information about the inductive potential of CAM can prevent undertreatment of cancer patients and unacceptable side effects resulting from increased activation of prodrugs.

**Nuclear Receptors**

Recently, orphan nuclear receptors involved in the induction of metabolizing enzymes and ABC drug transporters have been identified: the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), and the vitamin D-binding receptor (VDR). After activation by endogenous or exogenous ligands, these receptors form heterodimers with the 9-cis retinoic acid receptor (RXR) and bind to xenobiotic response elements in the target genes [32, 33]. Because of this, the transcription of the target genes is increased, leading to detoxification and elimination of xenobiots (Fig. 1).

PXR, also known as the steroid and xenobiotic receptor (SXR) [34] or human proteinase-activated receptor (hPAR) [40], has emerged as one of the main transcriptional regulators of CYP3A4 and Pgp [35, 36]. However, other metabolizing enzymes and drug transporters were also shown to be under transcriptional control of PXR: CYP2B6 [37], CYP2C9 [38], sulfortransferase (SULT) [39], UGT1A1 [40], glutathione S-transferases (GST) [41], and MRP-2 [42]. Currently known ligands of human PXR are all well-established inducers of CYP3A4, such as the drugs rifampicin, dexamethasone, clortrimazole, and paclitaxel [43, 44]. Moore et al. [45] showed that the inductive capacity of SJW is also mediated by PXR. SJW, in particular its active component hyperforin, activates PXR, thereby inducing CYP3A4 and CYP2C9 expression (Fig. 1) [38, 45]. Hyperforin was also shown to form a complex with the ligand-binding domain of human PXR [46]. These data indicate that the activation of PXR is one of the main mechanisms behind induction of metabolizing enzymes and drug transporters by CAM.

Another nuclear receptor identified to be involved in the induction of metabolizing enzymes is CAR. Although the CYP2B gene is the main target of CAR, expression of other hepatic genes, such as UGT1A1 and CYP2C9 among others, is also influenced by CAR [40, 47–49]. Very recently, it was shown that CAR is also involved in the regulation of the multidrug resistance gene 1 (MDR-1) [50].

While PXR was shown to mainly regulate CYP3A4 expression and CAR to regulate CYP2B expression, there is ample evidence that this specificity is not absolute and that both the nuclear transcription function as well as the ligand-binding capacity of these two receptors show some overlap. VDR is the receptor that normally mediates cell growth, differentiation, and death in response to 1α,25-dihydroxy vitamin D₃. Schmiedlin-Ren et al. [51] were the first to show that the VDR receptor is also involved in the regulation of CYP3A4, and currently it is known that VDR is also able to induce the expression of CYP2B6 and CYP2C9 [52]. Ligands of VDR are the already mentioned 1α,25-dihydroxy vitamin D₃ and also the secondary bile acid lithocholic acid, indicating an important role of VDR in the detoxification of hepatotoxic bile acids [53].

**Methods to Measure Induction and Activation of Nuclear Receptors by CAM**

The role of PXR, CAR, and VDR in the induction of metabolizing enzymes and drug transporters is now evident. Binding of CAM to any of these receptors can lead to increased metabolism or transport of coadministered chemotherapeutic drugs, leading to decreased therapeutic efficacy or increased toxicity of prodrugs. This knowledge has been applied to develop more specific methods to study the inductive capacity of CAM in vitro or in vivo model systems [54–58].

In the past, the fact that several compounds could induce metabolizing enzymes or drug transporters was recognized, and primary cultures of hepatocytes have been used for a long time to screen for the inductive potential of compounds. However, the main drawbacks of the use of human hepatocytes are the availability, quality, and interindividual variation of human liver tissue. Further, this system only gives information about the induction capacity and not about the nuclear receptor involved [54, 55, 58].

In vivo models, using wild-type laboratory animals, are not an alternative because of the observed species differences in the ligand-binding domains (LBDs), especially in the LBD of PXR. Alternatively, transgenic animals that possess human versions of nuclear receptors could be used [57].

Cloning of the human version of PXR [33–35] led to the development of competition binding assays and cell-based reporter assays (Fig. 2). In a cell-based reporter assay, expression plasmids for the specific full-length receptors, PXR, VDR, or CAR, are cotransfected with a relevant
reporter plasmid into a human cell line. This reporter plasmid contains either one or more copies of the response elements upstream of a heterologous promoter or an intact promoter of a target gene (e.g., CYP3A4), coupled to a reporter gene like alkaline phosphatase or luciferase [56, 59]. Advantages of the reporter gene assays are the use of inexpensive human-derived cell lines and the possibility to develop high-throughput formats. Reporter gene assays for PXR to assess the CYP3A4 induction potential of xenobiotics were proven to be reliable and complementary to the use of human hepatocytes [55].

These techniques can all be applied to test the inductive capacity of CAM, but ultimately, PK studies in patients using CAM will give a definite answer about the effects of CAM on the metabolism and excretion of chemotherapeutic drugs.

**Inductive Capacity of CAM**

Currently, data about the inductive capacity of CAM and their interaction with nuclear receptors is scarce and mainly focused on PXR. Further, there is a substantial lack of clinical information about the effect of CAM on the PK of anticancer drugs. The already mentioned interaction of SJW with PXR is the best-known example, and significant clinical effects of this interaction have already been shown, not only for anticancer drugs, but also for other drugs like amitriptyline, cyclosporine, and warfarin [60]. Still, some studies have been performed that investigated the effect of other CAMs on nuclear receptor-mediated CAM–drug interactions, and from those studies, possible effects of CAM on the PK of anticancer drugs can be derived.

**In Vitro**

In vitro studies have been performed to investigate the potential of CAM to activate nuclear receptors and to induce metabolizing enzymes. An overview of these studies is given in Table 3.

Raucy [61] used CYP3A4 mRNA analysis in primary cultures of human hepatocytes of 17 individuals to test the inductive properties of several flavonoids, including quercetin, resveratrol, and curcumin. Of these, only quercetin produced accumulation of CYP3A4 mRNA. However, when a reporter gene assay with hPXR was used, quercetin did not show a significant increase in luciferase activity, suggesting that CYP3A4 was induced by mechanisms not involving PXR. Herbs like grapeseed extract, ginseng, garlic, and kava-kava also increased CYP3A4 mRNA levels in hepatocytes, but of these botanicals, only kava-kava produced enhanced luciferase activity [61]. The results of that study clearly showed that some CAMs have the potential to induce CYP3A4, although not always mediated via PXR.

Individual forms of vitamin E also activate gene expression via PXR. Zhou et al. [62] found that α-, β-, γ-, and δ-tocotrienols, forms of vitamin E, but not α-, β-, γ-, and δ-tocopherols specifically bind to and activate PXR. In that study, it was shown, however, that the induction of target genes was tissue specific: upregulation of CYP3A4, but not UGT1A1 or MDR-1, in primary hepatocytes in contrast to increased UGT1A1 and MDR-1, but not CYP3A4, expression in intestinal LS180 cells [62]. Another study, also using a cell-based reporter system, showed that although α- and γ-tocotrienol showed the strongest inductive efficacy, δ-, α-, and γ-tocopherol could also activate PXR [63]. In that study, exposure of HepG2 cells to γ-tocotrienol gave an upregulation of endogenous CYP3A4 and CYP3A5 mRNA.

Other studies using gene reporter assays or mRNA levels of CYP3A4 in human hepatocytes showed the potential of several CAMs to induce CYP3A4 by activation of PXR: Gugulipid, or its chemical constituents guggulsterones, derived from the Mukul myrrh tree [64–67], hops [64], two traditional Chinese medicines (TCMs), Wu Wei Zi (Schisandra chinensis Baill) and Gan Cao (Glycyrrhiza uralensis Fisch), and their selective constituents [68], carotenoids, especially β-carotene, and retinol [69].

Flavonoids, like chrysin, induce UGT1A1 expression via another receptor, the aryl hydrocarbon receptor (AhR), which is beyond the scope of this review. However, PXR and CAR were also shown to contribute to the overall UGT1A1 response to flavonoids [70].

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**Figure 2.** Cell-based reporter assay. An expression plasmid containing the full-length receptor, pregnane X receptor (PXR), is cotransfected with a reporter plasmid into a human cell line. The reporter plasmid contains a PXR response element (PXRE) upstream of a reporter gene, luciferase or alkaline phosphatase. Upon binding of a ligand transcription of the reporter gene is increased and can be detected. (Based on Landes N, Pfuger P, Kluth D et al. Vitamin E activates gene expression via the pregnane X receptor. Biochem Pharmacol 2003;65:269–273; and Kliewer SA. Pregnan X receptor: Predicting and preventing drug interactions. Thromb Res 2005;117:133–136; discussion 145–151.)
Table 3. Potential of complementary and alternative medicines (CAM) to activate nuclear receptors and to induce metabolizing enzymes

<table>
<thead>
<tr>
<th>CAM</th>
<th>Method</th>
<th>Effect</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-carotene</td>
<td>CYP3A4 cell-based reporter assay with PXR mRNA expression in HepG2 cells</td>
<td>↑ CAT activity, ↑ CYP3A4/3A5, MDR-1, and MRP-2</td>
<td>Ruhl et al. [69]</td>
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<tr>
<td>Apigenin</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Ruhl et al. [69]</td>
</tr>
<tr>
<td>Apo-carotenals</td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ CAT activity</td>
<td>Ruhl et al. [69]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>No effect</td>
<td>Raucy [61]</td>
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<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Ruhl et al. [69]</td>
</tr>
<tr>
<td>Gan Cao (TCM)</td>
<td>CYP3A4, CYP2C9, and MRP-2 cell-based reporter assay with PXR</td>
<td>↑ luciferase activity</td>
<td>Mu et al. [68]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4, CYP2C9, and MRP-2 mRNA expression in human hepatocytes</td>
<td>↑ expression</td>
<td>Mu et al. [68]</td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetics of warfarin in rats</td>
<td>↓ t1/2, ↓ AUC, ↑ clearance</td>
<td>Mu et al. [68]</td>
</tr>
<tr>
<td>Garlic</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td>Ginseng</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Raucy [61]</td>
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<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td>Grapeseed extract</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Raucy [61]</td>
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<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Raucy [61]</td>
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<tr>
<td>Guggulsterone</td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ luciferase activity</td>
<td>Brobst et al. [65],</td>
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<td></td>
<td>CYP3A4 mRNA expression in human and rodent hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Owsley and Chiang [66]</td>
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<td></td>
<td>Protein interaction assay</td>
<td>Direct interaction with PXR</td>
<td>Brobst et al. [65]</td>
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<td></td>
<td>Pharmacokinetics of dihydroxy and pranaprolol in healthy volunteers</td>
<td>↓ C_{max}, ↓ AUC</td>
<td>Dalvi et al. [67]</td>
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<tr>
<td>Hops</td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ luciferase activity</td>
<td>Kliwe et al. [64]</td>
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<tr>
<td>Kava-kava</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Raucy [61]</td>
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<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ luciferase activity</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td>Lycopene</td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Ruhl et al. [69]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CYP3A4 mRNA</td>
<td>Raucy [61]</td>
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<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CAT activity</td>
<td>Ruhl et al. [69]</td>
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</tr>
<tr>
<td>Retinol</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CAT activity</td>
<td>Ruhl et al. [69]</td>
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<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ CYP3A4/3A5, MDR-1, and MRP-2</td>
<td>Ruhl et al. [69]</td>
</tr>
<tr>
<td>Silymarin</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No effect</td>
<td>Raucy [61]</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>↑ CAT activity for α and γ</td>
<td>Zhou et al. [62]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ CAT activity for α and γ</td>
<td>Landes et al. [63]</td>
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<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>Effective binding to PXR</td>
<td>Zhou et al. [62]</td>
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<td></td>
<td>CYP3A4 mRNA expression in primary hepatocytes</td>
<td>↑ CYP3A4, no effect on UGT1A1 or MDR-1</td>
<td>Zhou et al. [62]</td>
</tr>
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<td></td>
<td>mRNA expression in LS180 cells</td>
<td>↑ MDR-1, ↑ UGT1A1, no effect on CYP3A4</td>
<td>Zhou et al. [62]</td>
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<tr>
<td></td>
<td>mRNA expression in HepG2 cells</td>
<td>↑ CYP3A4/3A5 by γ</td>
<td>Landes et al. [63]</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>CYP3A4 mRNA expression in human hepatocytes</td>
<td>No effect</td>
<td>Zhou et al. [62]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>↑ CAT activity for α, β, γ</td>
<td>Landes et al. [63]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 cell-based reporter assay with PXR</td>
<td>No binding</td>
<td>Zhou et al. [62]</td>
</tr>
<tr>
<td>Wu Wei Zi (TCM)</td>
<td>CYP3A4, CYP2C9, and MRP-2 cell-based reporter assay with PXR</td>
<td>↑ luciferase activity</td>
<td>Mu et al. [68]</td>
</tr>
<tr>
<td></td>
<td>CYP3A4, CYP2C9, and MRP-2 mRNA expression in human hepatocytes</td>
<td>↑ expression</td>
<td>Mu et al. [68]</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the concentration–time curve; CAT, chloramphenicol acetyltransferase reporter gene activity; CYP, cytochrome P450; C_{max}, maximum observed concentration; MDR, multidrug resistance gene; MRP, multidrug resistance-associated protein; PXR, pregnane X receptor; t1/2, half-life; TCM, traditional Chinese medicine; UGT, uridine diphosphoglucuronosyl transferase.
In vivo

Although, because of species differences, in vivo models are not the best way to study induction of metabolizing enzymes and drug transporters, information can be obtained from them, especially when humanized transgenic animals are used [57]. In humanized CAR transgenic mice, it was shown that the TCM Yin Zhi Huang, a decoction of Yin Chin (Artemisia capillaris) and three other herbs, accelerates the clearance of bilirubin by activation of CAR [71]. Studies with wild-type rats showed induction of CYP2B by Ginkgo biloba extract [72], increased CYP3A expression and activity after exposure to licorice root extract and its natural constituent glycyrrhizin [73], and enhanced activity of GST and UGT after intake of rooibos (Aspalathus linearis) and honeybush (Cyclopia intermedi- dia) teas [74]. These studies, however, give no information about the mechanism behind the induction and the nuclear receptor involved. Careful interpretation of in vivo results is thus necessary because the species differences in nuclear receptors and inductive processes make extrapolation to humans difficult.

PK Studies in Humans

Besides the thorough investigation of the effects of SJW on the PK of drugs [75], only a few other clinical studies have been executed thus far that investigated interactions between other CAM and (anticancer) drugs.

Ginkgo biloba, one of the most widely used herbal products in the world, was shown to induce omeprazole hydroxylation in a CYP2C19 genotype-dependent manner in healthy male subjects. The authors therefore suggest that coadministration of Ginkgo biloba with omeprazole or other CYP2C19 substrates, like teniposide (Table 1), may significantly reduce their effects [76]. In two studies with healthy volunteers or elderly patients, Ginkgo biloba had no effect on the PK of model substrates for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 [77, 78].

In the same studies, there was also no significant effect observed on the activity of metabolizing enzymes after intake of garlic [77, 78]. Garlic intake also had no effect on the metabolism of acetaminophen [79] and on the PK of the protease inhibitor ritonavir in healthy volunteers [80]. However, intake by healthy volunteers of a higher dose of garlic did have a significant impact on the PK of another protease inhibitor, saquinavir [81]. In the presence of garlic, the mean AUC of saquinavir was 51% lower and the mean C_{max} was 54% lower. Although saquinavir is mainly metabolized by CYP3A4 and transported by Pgp, the discrepancy with the results obtained with model substrates and ritonavir suggests that the PK alterations with saquinavir are not a result of induction of CYP3A4 but more likely are a result of modulation of another enzyme or drug transporter. However, differences in the composition of the active constituents of the garlic supplements used could also explain variation in the clinical results. Therefore, patients are advised to use caution when combining garlic supplements with saquinavir, but also with anticancer drugs metabolized by CYP3A4 and transported by Pgp (Table 1, Table 2) [81].

Citrusaurantium, Panax ginseng, Echinacea purpurea, milk thistle, and saw palmetto extracts taken by healthy volunteers all had no effect on the activity of CYP3A4, CYP1A2, CYP2E1, and CYP3A4 measured using model substrates [77]. Milk thistle also did not influence the PK of the protease inhibitor indinavir in two independent studies [82, 83]. However, a recent study [84] showed that 8 days of echinacea treatment in volunteers resulted in a 34% greater systemic clearance of midazolam and a significantly lower AUC. In contrast, the oral bioavailability of midazolam after echinacea intake was significantly greater, indicating that there is a difference in the effect between hepatic and intestinal metabolism or drug transport. These data indicate that interactions of echinacea with anticancer drugs that are substrates of CYP3A4 is likely (Table 1).

Conclusion

As the intake of CAM is increasing, herb–drug interactions within oncology are likely to occur. In particular, lower therapeutic efficacy resulting from induction of metabolizing enzymes and drug transporters may not be easily recognized. It is therefore important that treating physicians are aware of the possibility of CAM–drug interactions. Unfortunately, the effects of CAMs on induction of metabolizing enzymes and drug transporters are generally not known and poorly studied. Some investigators have used probe substrates to explore the effects of herbs on the activity of specific CYP enzymes in healthy volunteers, like Gurley et al. [77]. Suitable substrates are caffeine for CYP1A2, tolbutamide for CYP2C9, mephentanyl for CYP2C19, dextrometorphan or debrisoquin for CYP2D6, and midazolam or erythromycin for CYP3A4. In addition, a cocktail of probe drugs can be used to explore the activities of multiple CYP enzymes [19]. From these type of studies, the physician already could derive specific recommendations for the use of various herbs in combination with chemotherapeutic treatment. However, phenotyping studies do have some limitations, such as marked intrasubject and intersubject variability and the possibility of interaction between coadministered probes [19]. Another disadvantage is the fact that, in most of these studies, herbs were used for a relatively short period of time, while for induction, in particular, chronic use is important. Another point of concern is the extrapolation
of data obtained in healthy volunteers using probe substrates to cancer patients using chemotherapeutic drugs. However, based on the information currently available from these and other types of studies, care should be taken with the combination of anticancer drugs and SJW, grapefruit juice, vitamin E, quercetin, ginseng, garlic, β-carotene, and echinacea, as these CAMs all have the potency to induce metabolizing enzymes and might cause under-treatment or greater toxicity in the case of prodrugs.

The discovery of the role of the nuclear receptors PXR, CAR, and VDR can be an aid in developing new methods to study the inductive potential of CAM. The difficulty lies in the fact that, in general, CAMs are mixtures of more than one active ingredient and are often of variable and undefined composition. Another important aspect is the fact that some CAMs might be antagonists of nuclear receptors, as was shown for the anticancer drug ET-743, which antagonizes PXR [36]. Currently, this phenomenon and the consequences thereof have not yet been studied for CAM. More attention should also be paid to the other receptors, CAR and VDR, as these are also an integral part of the mechanism of inductive processes. In the end, there is almost no information about whether the commonly applied dose range of CAM is critical for anticancer drug interactions in patients. Evaluation of the data obtained with in vitro and in vivo methods in well-designed clinical trials is therefore of utmost importance. Further research is therefore required and has to be encouraged to elucidate the role of CAM in unwanted drug interactions to prevent undertreatment of cancer patients or unexpected toxicities, and to establish guidelines for CAM use. For now, oncologists have to be encouraged to discuss CAM use with their patients and to be aware of possible CAM–anticancer drug interactions. In some cases, especially with the well-studied SJW, physicians should advise patients to refrain from their CAM use.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.

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ADDITIONAL READING


