J Endocrinol Reprod 12 (2008) 1: 1-12 **Review Article**

Clinical correlates in drug-herbal interactions mediated *via* nuclear receptor PXR activation and cytochrome P450 induction

Seema Negi[1], Mohammad A. Akbarsha[2] and Rakesh K. Tyagi[1]
[1]Special Centre for Molecular Medicine, Jawaharlal Nehru University
New Delhi – 110067, India
[2]Department of Animal Science, School of Life Sciences, Bharathidasan University
Tiruchirappalli - 620 024, India

This article is dedicated to the memory of Late Prof. Ben M.J. Pereira of Indian Institute of Technology, Roorkee, who had been actively associated with SRBCE and the Journal of Endocrinology and Reproduction

Summary

Pregnane and Xenobiotic Receptor (PXR), a vital xenosensor, acts as master regulator of phase-I (cytochrome P450) and phase-II enzymes (glutathione *S*-transferases, sulfotransferases, and uridine 5'-diphosphate glucuronosyltransferases) as well as several drug transporters (multi-drug resistance protein, and multi-drug resistance-associated protein). PXR can bind to a variety of chemically distinct endobiotics (steroids, bile acids and their derivatives, vitamins, etc.) and xenobiotics (prescription drugs, herbal medicines, endocrine disruptors, etc.). Activation of PXR by various compounds leads to trans-activation of PXR-target genes involved in detoxification system (phase-I and phase-II enzymes, and efflux proteins). Herbal medicines are readily used without prescription under the belief that anything natural is safe. These medicines contain active chemical constituents which execute distinctly different or similar pharmacological response(s). But, like prescription drugs, herbal drugs also have both therapeutic and, sometimes, adverse effects. Some of the herbal drugs induce drug metabolizing enzymes (especially CYP3A4) and drug efflux proteins *via* activation of PXR. Phase-I enzyme CYP3A4 is involved in the metabolism of 50-60% of clinical drugs as well as the chemical ingredients in herbal medicines. In addition to this, 25-30% of these compounds are metabolized by the CYP2B isoenzymes. The combined metabolic effects of phase-I and phase-II enzymes and drug transporters, following induction by therapeutic molecules, constitute the molecular basis for many drug-herbal interactions. For example, if one drug activates PXR, it can encourage the elimination of a co-administered drug that is also metabolized and eliminated by PXR-target gene products, thereby affecting the therapeutic efficacy of the drug in the context of combination therapy. The present review highlights some of the recent clinical correlates in drug-herbal interactions mediated primarily *via* PXR and cytochrome P450.

Keywords: Drug-herbal interactions, Pregnane and Xenobiotic Receptor (PXR), cytochrome P450 (CYP450), drug transporters.

1. Introduction

The history of herbal medicines is as old as human civilization. The documents, many of which are of great antiquity, reveal that plants were used as medicines in China, India, Amazon Basin, Egypt and Greece, long before the beginning of the Christian era. India is very rich in natural resources and traditional knowledge. The use of plants as a source of herbal medicine has been an innate and vital aspect of India's healthcare system. The three Indian traditional systems of medicine (Ayurveda, Siddha and Unani) have identified more than 1,500 medicinal plants, of which nearly 700 are commonly used (Agarwal and Raju, 2006). According to an estimate by the World Health Organization (WHO), 70-80% of the world population, especially in developing countries, relies on traditional medicines, mostly plant drugs, for their primary healthcare needs (WHO, 2002; Agarwal and Raju, 2006). Recent reports reveal that the worldwide market of herbal medicines is estimated to be around US $80 to 100 billion, and it is projected to reach up to US $2,500 billion by the year 2010 (Mathur, 2003; Agarwal and Raju, 2006).

Correspondence to be addressed to: Rakesh K. Tyagi, Ph.D., E-mail: rktyagi@yahoo.com; rkt2300@mail.jnu.ac.in

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

Herbal ingredients are readily used by millions of people without prescription under the belief that anything natural is safe. Like allopathic (prescription) drugs, herbal medicines also have different pharmacokinetic and pharmacodynamic properties which ultimately lead to produce therapeutic responses, but sometimes cause adverse actions and/or drug-herbal interactions. The concurrent use of herbal medicines and conventional (prescription) drugs by patients suffering from different diseases has progressively increased. Co-administration of herbal medicines with conventional drugs increases the risk of undesirable interactions between the two. Recently, St. John's wort (*Hypericum perforatum*), a herbal drug traditionally used as a natural treatment for depression, represented a highlighted case that warranted its safety evaluation (Brazier and Levine, 2003). Many of the compounds present in herbal medicines can potentially interact with the co-administered conventional drugs, causing either serious side effects or decreased pharmacological effect of the conventional drugs of narrow therapeutic index. Although the consumption of herbal health supplements along with prescription drugs is increasing globally, adequate information is not available on the mechanisms and consequences of drug-herbal interactions.

Drug-herbal interactions can occur at the pharmaceutical, pharmacodynamic or pharmacokinetic (PK) levels (Beijnen and Schellens, 2004) but most of the interactions occur at PK level (Brazier and Levine, 2003) that involves changes in absorption, distribution, metabolism and excretion of the conventional drug, which in turn determine the bioavailability of the drug. The metabolism of conventional drugs involves phase I enzymes such as cytochrome P450 family (CYP) or phase II enzymes, especially glutathione *S*-transferases (GST), sulfotransferases (SULT) and uridine 5'-diphosphate glucuronosyltransferases (UGT). These drug metabolizing enzymes and drug transporters, especially multi-drug resistance protein (MDR) and multi-drug resistance-associated protein (MRP), are regulated by the nuclear receptors (NR) such as Pregnane and Xenobiotic Receptor (PXR), Constitutive Androstane Receptor (CAR), and Vitamin D-binding Receptor (VDR) (Meijerman et al., 2006). Binding of a herbal constituent as ligand to any of these receptors activates or inhibits their transcriptional activity which would increase or decrease the metabolism or transport of the co-administered conventional drug(s) and lead to decreased therapeutic efficacy or increased toxicity of the drugs. Of the three NRs, PXR, also known as the Steroid and Xenobiotic Receptor (SXR) (Blumberg et al, 1998), is the molecule in focus for this review article. The emphasis of the present review is first on the modulation of PXR by active herbal compounds, and second on the interaction of active herbal compounds with prescription drugs *via* PXR-modulated detoxification machinery. The drug-herbal interactions with the involvement of PXR-mediated regulation of phase-I enzymes, phase-II enzymes and drug efflux proteins (drug transporters) is the fundamental platform of the discussion.

PXR is a novel ligand-activated intracellular transcription factor belonging to the nuclear receptor super-family. PXR is structurally characterized by its four distinct domains i.e., an amino-terminal transactivation domain, a central DNA-binding domain (DBD), the hinge region, and a carboxy-terminal ligand-binding domain (LBD). Unlike other nuclear receptor orthologs, PXR ortholog shares less amino acid homology in the LBD, providing the possibility for marked variation in its activation profile across species. PXR plays an important role in the transcriptional regulation of various genes involved in xenobiotic detoxification (Synold et al., 2001; Maglich et al., 2002). It has been shown that about 40 genes are under PXR regulation (Maglich et al., 2002). PXR acts as master regulator of detoxification defence machinery, i.e., phase-I and phase-II enzymes, as well as several drug transporters (Kliewer, 2003). After activation by endogenous or exogenous ligands, PXR heterodimerizes with the 9-*cis* retinoic acid receptor (RXR), binds to the xenobiotic response elements of the target genes and modulates their expression, leading to detoxification and elimination of the xenobiotics. Other than its function as a vital xenosensor, PXR also plays a key role in the metabolism of endobiotics (steroids, bile acids and their derivatives, vitamins, etc.) and xenobiotics (synthetic drugs, herbal medicines, endocrine disruptors, etc.). Ligand-mediated transcriptional activation of PXR is one of the principal mechanisms underlying the induction of drug metabolizing enzymes and drug transporters that ultimately leads to interactions of co-administered drugs. Irrespective of its ligand-bound or ligand-free status, PXR is predominantly present in the nuclear compartment and associates with condensed chromosomes during all stages of mitosis (Saradhi et al., 2005). In addition to the role of PXR in detoxification, bile homeostasis (Saini et al., 2005) and bone metabolism, its role in cancer is also becoming apparent. Therefore, PXR appears to be an important and promiscuous xenosensor in human health and disease (Saradhi et al., 2006). After completing a decade, the research outcome of several new findings on PXR reveal the diverse role of PXR in normal physiological control and patho-

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

physiological situations. Additionally, other studies not only expound the involvement of PXR in drug-drug/herbal interactions *via* modulating detoxification defence machinery but also in designing safer therapeutic molecules (Staudinger et al., 2006; Pal and Mitra, 2006).

2. Molecular basis of drug-herbal interactions

The chemical constituents of herbs have the potential to interact with various classes of drugs. These interactions could be directly or indirectly mediated by induction or inhibition of enzymes involved in drug metabolism and drug efflux proteins (Maglich et al., 2002; Pal and Mitra, 2006). The primary mechanisms behind drug-herbal interactions involve either induction or inhibition of intestinal drug efflux pumps (efflux proteins such as P-glycoprotein and MRPs) and intestinal and hepatic metabolism by CYPs (Evans, 2000; Ioannides, 2002). PXR activation by various compounds modulates intestinal efflux proteins and intestinal and hepatic CYPs (especially CYP3A4) which results in altered drug concentrations in plasma, thereby, causing drug-drug interactions (Lehmann et al., 1998; Evans, 2000). Therefore, herbs which have the potential to modulate efflux proteins and CYP3A4 may cause drug-herbal interactions and alter bioavailability of therapeutic drugs (Fugh-Berman, 2000; Fugh-Berman and Ernst, 2001; Izzo and Ernst, 2001). Any inhibitory effect of herbs on efflux proteins and CYP3A4 may result in elevated level of plasma and tissue concentration of co-administered prescription drug that would lead to toxicity. On the other hand, the inductive effect may cause decrease in drug concentration that would lead to decrease in therapeutic efficacy and failure of treatment (Staudinger et al., 2001). These drug-herbal interactions and detoxification occur mainly in the intestine and liver simultaneously. Indirectly, PXR accounts for the breakdown of about half of the clinically used drugs by the activation of the main transcriptional regulators of CYP3A4 and P-glycoprotein which are extensively distributed in the human tissues such as liver, intestine, colon, lung, etc. (Blumberg et al., 1998).

However, other drug metabolizing enzymes and drug transporters that are shown to be under transcriptional control of PXR include CYP2B6 (Goodwin et al., 2001), CYP2C8, CYP2C9 (Synold et al., 2001), CYP3A4 (Lehmann et al., 1998), SULT, UGT 1A1, GST, MDR1 (Geick et al., 2001) and MRP2 (Kast et al., 2002). The enzyme CYP3A4 is involved in the metabolism of 50-60 % of clinical drugs as well as compounds in herbal medicines. In addition to this, 25-30 % of these compounds are metabolized by the CYP2B isoenzymes. The combined metabolic effects of CYP3A and CYP2B, upon their induction by xenobiotic substrates such as compounds in herbal drugs, constitute a molecular basis for many drug-herbal interactions (Pichard et al., 1996). For example, if one drug activates PXR, it can encourage the elimination of other co-administered drugs that are also metabolized and eliminated by PXR-target gene products, thereby reducing the therapeutic efficacy of many drugs in combination therapy (Fig. 1). Some of the constituents of herbal medicines implicated in drug-herbal interactions mediated *via* PXR are shown in Figure 2. Future studies are expected to include more herbal constituents to this list.

3. St. John's wort – Drug interactions

St. John's wort (*Hypericum perforatum*) is a herbal remedy widely used for the treatment of depression. The crude extract of St. John's wort contains a complex mixture of several active chemical constituents such as hypericin, quercetin, isoquercitin, biflavonoids, hyperforin, naphthodanthrones, procyanidines, catechin tannins, chlorogenic acid, etc. The principal compound responsible for antidepressant action of St. John's wort is hyperforin, the response of which is mediated primarily *via* inhibition of synaptic reuptake of neurotransmitters (serotonin, nor-epinephrine and dopamine) (Moore et al., 2000).

St. John's wort is an efficacious activator of PXR in cell-based reporter assays (Moore et al., 2000; Wentworth et al., 2000) and its activation induces hepatic drug metabolism (Moore et al., 2000). PXR activation leads to up-regulation of CYP3A4 expression and an increase in metabolism of CYP3A4 substrates (e.g., cyclosporin). St. John's wort has been shown to alter the expression and function of P-glycoprotein in animal and human subjects, resulting in decreased concentrations of drugs in plasma (e.g., digoxin) (Durr et al., 2000; Fugh-Berman and Ernst, 2001). St. John's wort is responsible for a number of clinically relevant drug interactions that reduce the efficacy of several therapies, such as in transplantation, AIDS, cancer, etc. It has also been shown that St. John's wort enhances the metabolism of a variety of prescription drugs. These include oral contraceptives, cyclosporine, digoxin, warfarin, indinavir and theophylline (Johne et al., 1999; Nebel et al., 1999; Breidenbach et al., 2000; Durr et al., 2000; Karliova et al., 2000; Mai et al., 2000; Piscitelli et al., 2000; Ruschitzka et al., 2000; Hennessy et al., 2002; Brazier and Levine, 2003). Several reports disclose around 80-85 drug-herbal interaction cases with St. John's wort, of which 54 cases were with the drug cyclosporine. Other drug categories interacting with St. John's wort are oral

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

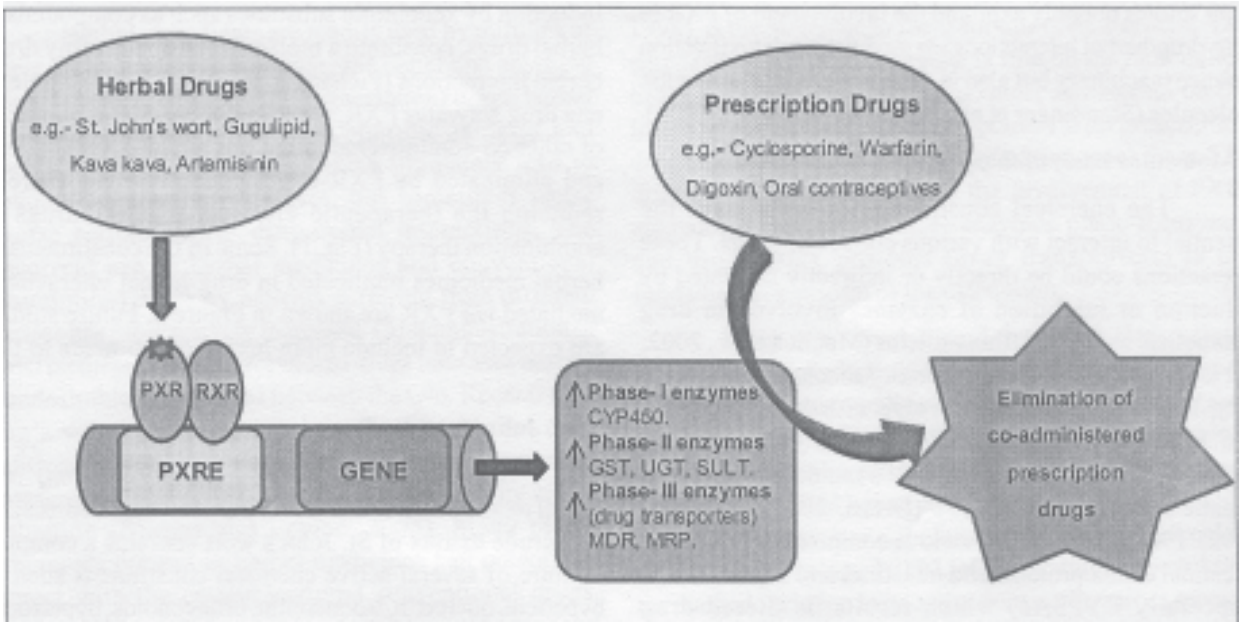

Fig. 1: Drug-herbal interactions mediated *via* PXR. PXR, upon activation by herbal drugs, heterodimerizes with RXR and subsequently binds to specific response elements, which ultimately leads to transcriptional regulation of the genes involved in metabolism and elimination *via* components of phase- I, phase- II and phase- III. Binding of herbal drugs to PXR and induction of detoxification machinery promotes metabolism and elimination of co-administered prescription (allopathic) drugs, which are the substrates for the metabolizing enzymes. Rapid clearance of prescription drugs results in reduced therapeutic efficacy of drugs used to treat different diseases. CYP450, Cytochrome P450; GST, Glutathione *S*-transferase; UGT, Uridine 5'-diphosphate glucuronosyltransferase; SULT, Sulfotransferases; MDR, Multi-drug resistance protein; MRP, Multi-drug resistance-associated protein.

contraceptives (12 cases), antidepressants (09 cases), warfarin (07 cases) and one case each with theophylline, phenprocoumon and loperamide (Kast et al., 2002). A recent study identified 37 cases of interactions for St. John's wort with digoxin (13 cases), clopidogrel (06 cases), indinavir (08 cases), irinotecan (05 cases), antipsychotics (03 cases), tacrolimus (01 case) and with an anesthetic (01 case) (Gokhil and Patel, 2007). Induction of drug metabolizing enzymes by St. John's wort lowers the plasma concentration of co-administered prescription drug. Similarly, prolonged intake of herbal supplement (inducer) may result in sub-therapeutic concentrations of co-administered drug (Pal and Mitra, 2006). All these reports indicate that St. John's wort is somewhat a risky proposition when combined with drugs in the categories mentioned above. Most of these drugs are metabolized by phase-I enzymes, especially CYP3A, and these interactions are mediated by the involvement of PXR. St. John's wort compounds bind to PXR, and strengthen the interaction between PXR and the steroid receptor co-activator 1 (SRC-1) (Wentworth et al., 2000). The findings suggest that structurally modified drugs that do not bind and activate PXR will be safer anti-depressants since unfavourable drug interactions can be prevented during co-administration of other drugs.

4. Mukul myrth – Drug interactions

Mukul myrth (*Commiphora mukul)* is an Ayurvedic medicine used to treat hyperlipidemia (Beg et al., 1996). The stereoisomers *E*- and *Z*-guggulsterone are the active constituents of gugulipid that diminish hepatic cholesterol levels (Singh et al., 1990; Urizar et al., 2002). The therapeutic effect of guggulsterone is believed to be mediated through the antagonism of the nuclear receptor Farnesoid X Receptor (FXR) (Urizar et al., 2002).

Recently, by using promoter-reporter assays it was shown that guggulsterone activates PXR. More over, gugulipid and guggulsterone treatments stimulate CYP3A4 gene expression through PXR in hepatocytes. Although this herbal drug produces desirable therapeutic effects in lipid disorders, it may cause adverse drug-herbal interactions on combination therapy through activation of

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

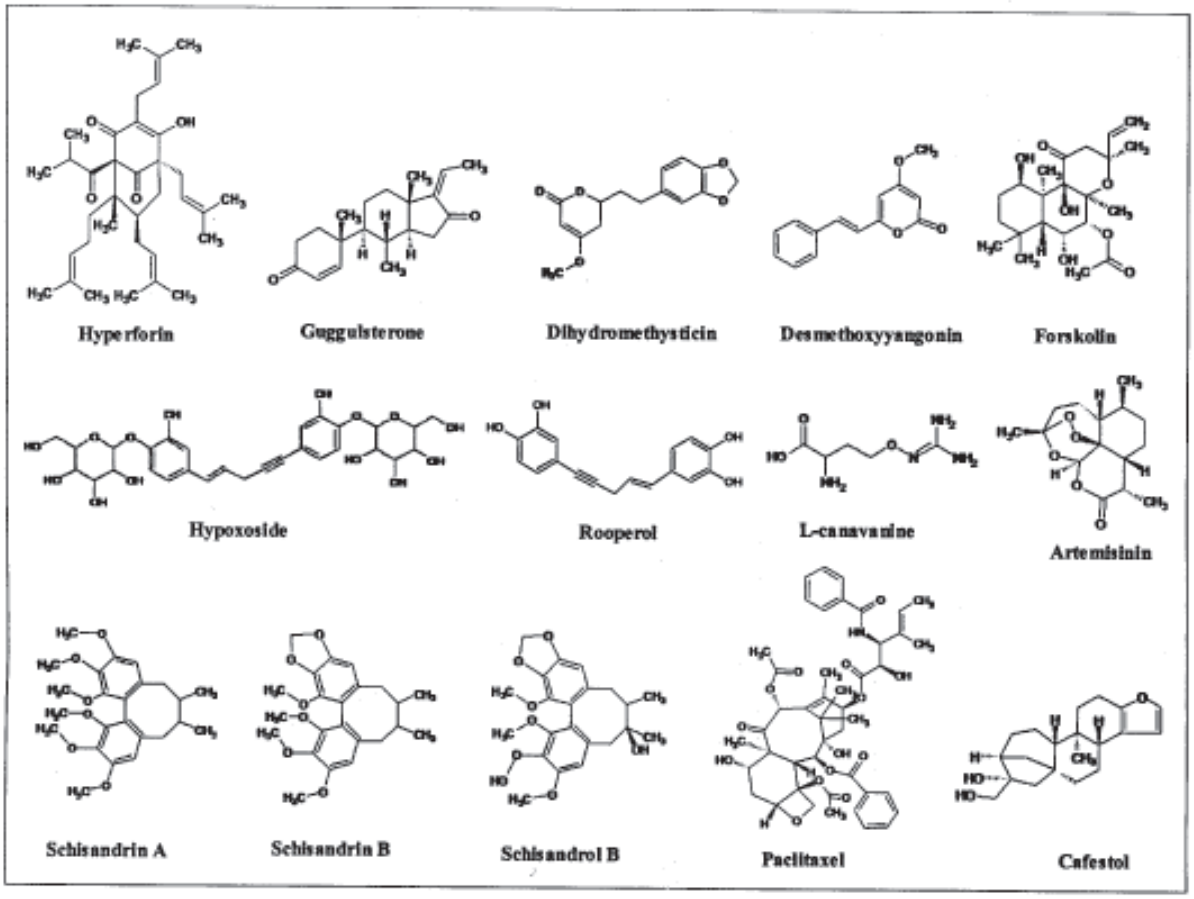

Fig. 2: Chemical structure of some of the active constituents of herbal medicines responsible for PXR-mediated drug-herbal interactions. This figure includes such active constituents as hyperforin (in St. John's wort), guggulsterone (in Mukul myrth), dihydromethysticin and desmethoxyyangonin (in Kava kava), forskolin **(**in *Coleus forskohlii)*; hypoxoside (an inactive constituent in *Hypoxis sp*, which is converted into active metabolite rooperol in the gut), L-canvanine (in *Sutherlandia sp*), artemisinin (in Qing hao), schisandrin A, schisandrin B and schisandrol B (in Wu wei zi), Paclitaxel, also called taxol (in Pacific yew), and cafestol (in coffee).

PXR. Protein interaction assays show that guggulsterone activates PXR by recruiting the co-activator SRC-1 (Brobst et al., 2004). The results of a well-controlled human study revealed that gugulipid interacts with prescription drugs such as diltiazem and propranolol and reduces their peak plasma concentrations (Dalvi et al., 1994). Studies have shown that guggulsterones not only activate FXR and PXR but also modulate the activity of multiple nuclear receptors, including CAR, glucocorticoid receptor, progesterone receptor, mineralocorticoid receptor, androgen receptor and estrogen receptor (Dalvi et al., 1994; Burris et al., 2005; Ding and Staudinger, 2005a).

5. Kava kava – Drug interactions

Kava kava (*Piper methysticum*) is a herbal remedy widely used as an anti-anxiety drug. It is also used to treat a wide variety of disorders including insomnia, stress, restlessness, muscle fatigue, gonorrhoea and vaginitis. The therapeutically important compounds in Kava kava are a group of structurally related lactones, collectively termed kavalactones. The effects of kavalactones are believed to be mediated by γ-aminobutyric acid (GABA) receptors in the central nervous system (CNS) (Jussofie et al., 1994). In addition to their effect on the CNS, kavalactones have been shown to modulate the activities of hepatic CYP enzymes. The activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are inhibited by kavalactones through a competitive mechanism (Mathews et al., 2002). Kavalactones, desmethoxyyangonin and dihydromethysticin, activate PXR in reporter gene assays but with lesser efficacy as compared to the classical PXR

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

agonist rifampicin. These two kavalactones are responsible for the induction of CYP3A23 gene expression mediated *via* PXR activation. Kava kava exerts dual effects on CYP enzyme: (i) competitive inhibition, and (ii) induction of CYP3A gene expression. Both these kava lactones affect the therapeutic efficacy of co-administered drugs such as levodopa, hydrochlorthiazide, promethazine, fluspirilen and biperiden (Ma et al., 2004). All these reports suggest that Kava kava would affect the metabolism of co-administrated drugs in a manner similar to St. John's wort.

6. *Coleus forskohlii* – Drug interactions

The extract of plant *Coleus forskohlii* has been used as an Ayurvedic medicine to treat various disorders including hypothyroidism, hypertension, congestive heart failure, eczema, respiratory disorders and convulsions (Ammon and Muller, 1985). It is also known to be used as an anti-obesity agent, in view of its 'fat burning' property. The two diterpene compounds forskolin and 1, 9-dideoxyforskolin are the active constituents of *C. forskohlii*. Forskolin has both cAMP-dependent and cAMP-independent activities. Forskolin is widely used as a biochemical tool to activate adenyl cyclase and increase intracellular concentration of cAMP with subsequent activation of protein kinase A (PKA) signal transduction pathway (Seamon et al., 1981). It was shown that both forskolin and 1, 9 dideoxyforskolin (non-adenylcyclase activating analog) induce CYP3A gene expression in primary cultures of rodent hepatocytes (Sidhu and Omiecinski, 1996). Recent studies reveal that both these compounds are potent PXR activators (Ding and Staudinger, 200; Dowless et al., 2005), which work by displacing the co-repressor N-CoR and recruiting co-activators such as SRC-1. Forskolin, 1, 9-dideoxyforskolin and *C. forskohlii* extract produce PXR-mediated induction of CYP3A. In addition to this, activation of PKA signal transduction pathway potentiates PXR-mediated xenobiotic response as well as interaction between PXR and known co-activator proteins in cell-based assays. Interestingly, PKA and PXR signalling pathways have a synergistic effect on the induction of CYP3A gene expression in primary mouse hepatocyte cultures (Ding and Staudinger, 2005b). Consumption of *C. forskohlii* extract is not advised with anti-hypertensives and anti-coagulants due to the high potential for drug-herbal interactions.

7. *Hypoxis*- and *Sutherlandia* – Drug interactions

Hypoxis hemerocallidea and *Sutherlandia frutescens* are African herbal and traditional remedies used for HIV treatment (Mills et al., 2005a). Both the herbs are recommended by the South African Ministry of Health for HIV therapy but the molecular mechanisms underlying their therapeutic effects are not yet known. An important biologically active compound in *H. hemerocallidea*, hypoxoside, is responsible for the medicinal property, which readily converts to aglycone rooperol in the human gut (Albrecht et al., 1995). The principal constituents of *S. frutescens* include L-canavanine, GABA and D-pinitol. L-canavanine is responsible for the anti-viral effects.

Recent *in vitro* experiments indicate that crude extracts of both the herbs inhibit CYP3A4 activity and P-glycoprotein expression while activate PXR. The findings suggest that co-administration of these herbal drugs with other drugs results in inhibition of drug metabolism and transport during short term therapy. However, prolonged therapy results in induction of the same detoxification machinery. This observation is exemplified with an anti-retroviral agent (Mills et al., 2005b). It remains to be determined if the active herbal compounds in the extracts affecting CYP3A4 and PXR are different from those having therapeutic activities and, if so, the compounds with potential therapeutic activities could be purified to treat patients and avoid unwanted side effects caused by CYP3A4 and PXR intervention.

8. Qing hao – Drug interactions

Qing hao (*Artemisia annua*) is a Chinese herbal medicine used in treatment of malaria. The therapeutically active compound it contains is artemisinin (or qinghaosu). Artemisinin and some of its active synthetic derivatives (artemether, arteether and artesunate), collectively called artemisinin drugs, are used worldwide as effective and popular anti-malarial drugs because the malarial parasite has not yet developed resistance against these drugs (van Agtmael et al., 1999). But, then, allopathic drugs co-administered with artemisinin drugs will result in lowered plasma concentration and decreased therapeutic efficacy of the allopathic drugs due to induction of detoxification machinery (Hassan Alin et al., 1996; Ashton et al., 1998). This inference is based on the fact that artemisinin activates PXR and CAR in reporter gene assays and also known to induce CYP2B6, CYP3A4 and MDR1 gene expressions in primary human hepatocytes and the human intestinal cell line LS174T (Burk et al., 2005). These findings reveal that artemisinin has a higher risk of potential drug-herbal interactions *via* induction of CYP3A4 and MDR1 through activation of PXR and CAR.

9. Wu wei zi – Drug interactions

Wu wei zi (*Schisandra chinensis),* a traditional Chinese medicine, means 'five-flavor fruit' in Chinese since

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

it has all the five basic flavors: salty, sweet, sour, pungent (spicy) and bitter. It has been already reported that Wu wei zi extracts and the active chemical constituents, including schisandrin A, schisandrin B and schisandrol B are potent PXR agonists in reporter gene assays. Its hepato-protective effects are clinically documented and used for treatment of many ailments such as infections, cough and thirst. The therapeutically active hepato-protective and immuno-modulating constituents are the lignans, schisandrin, deoxyschisandrin, gomisins and pregomisin. In addition to PXR activation, these constituents efficaciously induce the PXR target genes CYP3A4 and CYP2C9 in primary cultures of human hepatocytes and promote *in vivo* drug metabolism (Mu et al., 2006). It has also been shown that Wu wei zi increases the metabolism of co-administered drug warfarin in rat. Although the herb has hepato-protective property, it may cause drug-herbal interactions due to induction of detoxification system.

10. Gan cao (Licorice) – Drug interactions

Gan cao (*Glycyrrhiza uralensis*) is another traditional Chinese medicine that has anti-inflammatory and hepato-protective effects. It activates PXR (Mu et al., 2006) but it remains to be determined if it would induce PXR target genes. Like Wu wei zi, Gan cao also promotes *in vivo* drug metabolism and increases metabolism of warfarin in rats. The activation of PXR by this herb may also provide beneficial effects because of hepato-protective action. One study has shown that PXR activation promotes bilirubin detoxification in mice (Synold et al., 2001). These studies highlight the dual nature of PXR activation: i) the promotion of drug metabolism, leading to potential drug interactions and therapeutic failure, and ii) activation of detoxifying systems to protect our bodies from toxic insults.

11. Paclitaxel – Drug interactions

Paclitaxel (Taxol), a member of the taxane family of anti-microtubule agents, is isolated from the bark of the Pacific yew (*Taxus brevifolia*) and widely used in the treatment of several types of cancer such as ovarian, breast and lung carcinomas. Paclitaxel is metabolically inactivated by the hepatic cytochrome P450 enzymes CYP3A4 and CYP2C8. Both these enzymes hydroxylate paclitaxel thereby abolishing the anti-mitotic properties of the drug. In addition, paclitaxel is excreted from the intestine *via* P-glycoprotein efflux pump protein encoded by the gene MDR1 (Synold et al., 2001). Gene-targeting studies have demonstrated that P-glycoprotein is responsible for excretion of 85% of the orally administered paclitaxel. Earlier reports have shown that paclitaxel is an effective inducer of CYP3A expression in primary cultures of rat and human hepatocytes (Kostrubsky et al., 1997, 1998). Furthermore, investigations employing cell-based reporter assays have shown that paclitaxel strongly activates human PXR (Synold et al., 2001; Nallani et al., 2004). Mammalian two-hybrid assays revealed that paclitaxel-bound PXR recruits nuclear receptor co-activators and displaces co-repressors. The Northern blot analysis in this study showed that paclitaxel induces the expression of CYP2C8, CYP3A4 and MDR1 in hepatocytes (Synold et al., 2001). These results were confirmed *in vivo* by employing PXR-null mice (Nallani et al., 2003). In view of these findings, the herbal drug paclitaxel could be a suspect in drug-herbal interactions.

12. Cafestol– Drug interactions

Coffee bean (*Coffea arabica*) is a herbal remedy widely used as CNS stimulant and as an anti-diuretic agent. It contains several active chemical constituents such as caffeine, cafestol, kahweol, etc. Cafestol, a diterpene, is the most potent cholesterol-elevating compound in coffee beans and may also act as an anti-carcinogen. Cafestol is abundantly present in unfiltered coffee brews as compared to espresso coffee. It is already known that PXR can also inhibit CYP7A1 expression (Staudinger et al., 2001), and is activated by a variety of xenobiotics, and thus protects the liver from toxic compounds (Goodwin et al., 2003). It is also known that certain bile acids can inhibit CYP7A1 expression independently of small heterodimer partner (SHP) *via* PXR (Kerr et al., 2002; Wang et al., 2002; Saradhi et al., 2006). In this background, cafestol has been shown to regulate metabolic and detoxification genes in mice. It activates mouse and human PXR as well as FXR in the reporter-based transactivation assay. Cafestol enhances interaction of PXR with nuclear receptor coactivator SRC-1 and induces CYP3A4 promoter activity *via* PXR but to a lesser extent than its known ligand, rifampicin (Ricketts et al., 2007). Cafestol also induces the activity of several GST enzymes (Lam et al., 1982, 1987) and, therefore, is a potential suspect for drug-herbal interactions.

13. β-Carotene – drug interactions

β-Carotene belongs to the group of carotenoids and exhibits pro-vitamin A activity. Its major sources are green, yellow, orange and red vegetables. Tomatoes, spinach, carrots, apricot, grapefruit, cherry and papaya are rich in **β**-carotene. **β**-Carotene is endogenously present as several isomers: all trans–**β**, **β**´-carotene, the major

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

β-carotene isomer, followed by 15-*cis*, 13 *cis*- and 9-*cis* - isomers (Stahl et al., 1992). Earlier studies adopting reporter cell assay have revealed that β-carotene is an activator of the human PXR even at physiological concentrations found in human plasma and organs. β-Carotene brings about PXR-mediated induction of drug metabolizing enzymes CYP3A as well as drug transporters MDR1 and MRP2 (Rühl et al., 2004). Induction of CYP3A genes and drug efflux proteins can increase the drug clearance and reduce the therapeutic efficacy of co-administered pharmaceutical drugs, ultimately causing drug-herbal interactions (Pal and Mitra, 2006).

14. Conclusions

Herbal medicines contain a number of active constituents exhibiting different or similar pharmacological effects. However, in certain instances, some of the active constituents of herbal medicines are implicated in causing drug-herbal interactions when co-administered with allopathic drugs. For examples, in certain clinical situations co-administration of herbal medicines with prescription drugs may modulate the pharmacological activity of the co-administered drug. Here we have provided an overview, on the basis of available evidences, indicating that herbal medicines have the potential to cause clinically significant life-threatening drug-herbal interactions. Some of the herbal medicines responsible for the activation of phase-I and phase-II drug metabolizing enzymes and phase-III drug transporters, regulated *via* PXR, are now identified. From the comprehensive evidences of drug-herbal interaction, it is clear that the herbal medicines, which patients receive, can potentially interfere with prescription drugs by activation of drug metabolizing enzymes *via* PXR, and such patients are most at risk of serious drug-herbal interactions. Patients generally consider herbal medicines as safe and may not mention their intake during medication history interviews performed by pharmacists, nurses or physicians. In view of the current understanding, patients should be enquired about any intake of herbal medicines or natural product(s) and other medications in order to evaluate the potential of these products to interfere when used concurrently with prescription medication. More importantly, in the perspective of PXR's role, there is need for more *in vivo* studies to validate drug-herbal interactions and determine the clinical importance of drug-herbal interactions from the holistic viewpoint (Venkataramanan et al., 2006). Drug assays in correlation with PXR can serve as a valuable tool to assess and prevent potential drug-herbal interactions. It is strongly recommended that herbal remedy when used in combination with other drugs should be evaluated, monitored and screened to prevent possible interactions with prescription medications. A comprehensive approach and understanding will help combating undesired clinical complications.

Acknowledgments

The research work in our laboratory (JNU) on PXR is financially supported by research grants to RKT from Department of Science and Technology (SR/SO/BB-17/2006) and Council of Scientific and Industrial Research [37(1249)/06/EMR-II].

References

Agrawal OP, Raju PS. (2006) Traditional system of medicine. In: Abdin MZ and Abroi YP (Eds) *Global Market of Herbal Products: Opportunities for India*. Pp 5-10. Narosa Publishing House, New Delhi, India.

Albrecht CF, Kruger PB, Smit BJ, Freestone M, Gouws L, Miller R, van Jaarsveld PP (1995) The pharmacokinetic behaviour of hypoxoside taken orally by patients with lung cancer in a phase I trial. *S Afr Med J* 85: 861-865.

Ammon HP, Muller AB (1985) Forskolin: From an ayurvedic remedy to a modern agent. *Planta Med* 6: 473-477.

Ashton M, Hai TN, Sy ND, Huong DX, Van Huong N, Niêu NT, Công LD (1998) Artemisinin pharmacokinetics is time-dependent during repeated oral administration in healthy male adults. *Drug Metab Dispos* 26: 25-27.

Beg M, Singhal KC, Afzaal S (1996) A study of effect of guggulsterone on hyperlipidemia of secondary glomerulopathy. *Indian J Physiol Pharmacol* 40:237-240.

Beijnen JH, Schellens JH (2004) Drug interactions in oncology. *Lancet Oncol* 5: 489-496.

Blumberg B, Sabbagh WJ, Juguilon H, Bolado JJ, van Meter CM, Ong ES, Evans RM (1998) SXR, a novel steroid and xenobiotic-sensing nuclear receptor. *Genes Dev* 12: 3195–3205.

Brazier NC, Levine MA (2003) Drug-herb interaction among commonly used conventional medicines: a compendium for health care professionals. *Am J Ther* 10: 163-169.

Breidenbach T, Hoffmann MW, Becker T, Schlitt H, Klempnauer J (2000) Drug interaction of St John's wort with cyclosporine. *Lancet* 355: 1912.

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

Brobst DE, Ding X, Creech KL, Goodwin B, Kelley B, Staudinger JL (2004) Guggulsterone activates multiple nuclear receptors and induces CYP3A gene expression through the pregnane X receptor. *J Pharmacol Exp Ther* 310: 528-535.

Burk O, Arnold KA, Nussler AK, Schaeffeler E, Efimova E, Avery BA, Avery MA, Fromm MF, Eichelbaum M (2005) Antimalarial artemisinin drugs induce cytochrome P450 and MDR1 expression by activation of xenosensors pregnane X receptor and constitutive androstane receptor. *Mol Pharmacol* 67: 1954-1965.

Burris TP, Montrose C, Houck KA, Osborne HE, Bocchinfuso WP, Yaden BC, Cheng CC, Zink RW, Barr RJ, Hepler CD, Krishnan V, Bullock HA, Burris LL, Galvin RJ, Bramlett K, Stayrook KR (2005) The hypolipidemic natural product guggulsterone is a promiscuous steroid receptor ligand. *Mol Pharmacol* 67: 948-954.

Dalvi SS, Nayak VK, Pohujani SM, Desai NK, Kshirsagar NA, Gupta KC (1994) Effect of gugulipid on bioavailability of diltiazem and propranolol. *J Assoc Physicians India* 42: 454-455.

Ding X, Staudinger JL (2005a) The ratio of constitutive androstane receptor to pregnane X receptor determines the activity of guggulsterone against the Cyp2b10 promoter. *J Pharmacol Exp Ther* 314: 120-127.

Ding X, Staudinger JL (2005b) Induction of drug metabolism by forskolin: the role of the pregnane X receptor and the protein kinase a signal transduction pathway. *J Pharmacol Exp Ther* 312: 849-856.

Dowless MS, Barbee JL, Borchert KM, Bocchinfuso WP, Houck KA (2005) Cyclic AMP-independent activation of CYP3A4 gene expression by forskolin. *Eur J Pharmacol* 512: 9-13.

Durr D, Stieger B, Kullak-Ublick G, Rentsch K, Steinert H Meier P, Fattinger K (2000) St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 68: 598-604.

Evans AM (2000) Influence of dietary components on the gastrointestinal metabolism and transport of drugs. *Ther Drug Monit* 22: 131-136.

Fugh-Berman A (2000) Herb–drug interactions. *Lancet* 355: 134–138.

Fugh-Berman A, Ernst E (2001) Herb–drug interactions: Review and assessment of report reliability. *Br J Clin Pharmacol* 52: 587–595.

Geick A, Eichelbaum M, Burk O (2001) Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. *J Biol Chem* 276: 14581-14587.

Gokhil KJ, Patel JA (2007) Herb-drug interactions: A review and study based on assessment of clinical case reports in literature. *Indian J Pharmacol* 39: 129-139.

Goodwin B, Moore LB, Stoltz CM, McKee DD, Kliewer SA (2001) Regulation of the human CYP2B6 gene by the nuclear pregnane X receptor. *Mol Pharmacol* 60: 427-431.

Goodwin B, Gauthier KC, Umetani M, Watson MA, Lochansky MI, Collins JL, Leitersdorf E, Mangelsdorf DJ, Kliewer SA, Repa JJ (2003) Identification of bile acids precursors as endogenous ligands for the nuclear xenobiotic pregnane X receptor. *Proc Natl Acad Sci USA* 100: 223–228.

Hassan Alin M, Ashton M, Kihamia CM, Mtey GJ, Björkman A (1996) Multiple dose pharmacokinetics of oral artemisinin and comparison of its efficacy with that of oral artesunate in falciparum malaria patients. *Trans R Soc Trop Med Hyg* 90: 61-65.

Hennessy M, Kelleher D, Spiers J, Barry M, Kavanagh P, Back D, Mulcahy F, Feely J (2002) St Johns wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 53: 75-82.

Ioannides C (2002) Pharmacokinetic interactions between herbal remedies and medicinal drugs. *Xenobiotica* 32: 451–478.

Izzo AA, Ernst E (2001) Interactions between herbal medicines and prescribed drugs: A systematic review. *Drugs* 61: 2163–2175.

Johne A, Brockmoller J, Bauer S, Maurer A, Langheinrich M, Roots I (1999) Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther* 66: 338– 345.

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

Jussofie A, Schmiz A, Hiemke C (1994) Kavapyrone-enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. *Psychopharmacology (Berl)* 116: 469-474.

Karliova M, Treichel U, Malago M, Frilling A, Gerken G, Broelsch CE (2000) Interaction of *Hypericum perforatum* (St. John's wort) with cyclosporine A metabolism in a patient after liver transplantation. *J Hepatol* 33: 853–855.

Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliewer S, Willson TM, Edwards PA (2002) Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* 277: 2908-2915.

Kerr TA, Saeki S, Schneider M, Schaefer K, Berdy S, Redder T, Shan B, Russell DW, Schwarz M (2002) Loss of nuclear receptor SHP impairs but does not eliminate negative feedback regulation of bile acid synthesis. *Dev Cell* 2: 713–720.

Kliewer SA (2003) The nuclear pregnane X receptor regulates xenobiotic detoxification. *J Nutr* 133: 2444S-2447S.

Kostrubsky VE, Lewis LD, Wood SG, Sinclair PR, Wrighton SA and Sinclair JF (1997) Effect of Taxol on cytochrome P450 3A and acetaminophen toxicity in cultured rat hepatocytes: comparison to dexamethasone. *Toxicol Appl Pharmacol* 142: 79-86.

Kostrubsky VE, Lewis LD, Strom SC, Wood SG, Schuetz EG, Schuetz JD, Sinclair PR, Wrighton SA and Sinclair JF (1998) Induction of cytochrome P4503A by taxol in primary cultures of human hepatocytes. *Arch Biochem Biophys* 355: 131-136.

Lam LK, Sparnins VL, Wattenberg LW (1982) Isolation and identification of kahweol palmitate and cafestol palmitate as active constituents of green coffee beans that enhance glutathione S-transferase activity in the mouse. *Cancer Res* 42: 1193–1198.

Lam LK, Sparnins VL, Wattenberg LW (1987) Effects of derivatives of kahweol and cafestol on the activity of glutathione S-transferase in mice. *J Med Chem* 30: 1399–1403.

Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA (1998) The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* 102: 1016–1023.

Ma Y, Sachdeva K, Liu J, Ford M, Yang D, Khan IA, Chichester CO, Yan B (2004) Desmethoxyyangonin and dihydromethysticin are two major pharmacological kavalactones with marked activity on the induction of CYP3A23. *Drug Metas Dispos* 32: 1317-1324.

Maglich JM, Stoltz CM, Goodwin B, Hawkins-Brown D, Moore JT, Kliewer SA (2002) Nuclear pregnane X receptor and constitutive androstane receptor regulate overlapping but distinct sets of genes involved in xenobiotic detoxification. *Mol Pharmacol* 62: 638–646.

Mai I, Kruger H, Budde K, Johne A, Brockmoller J, Neumayer HH, Roots I (2000) Hazardous pharmacokinetic interaction of Saint John's wort (*Hypericum perforatum*) with the immunosuppressant cyclosporin. *Int J Clin Pharmacol Ther* 38: 500-502.

Mathews JM, Etheridge AS, Black SR (2002) Inhibition of human cytochrome P450 activities by kava extract and kavalactones. *Drug Metab Dispos* 30: 1153-1157.

Mathur A (2003) Who owns traditional knowledge*? Indian Council for Research on International Economic Relations Working Paper* 96: 1-33.

Meijerman I, Beijnen JH, Schellens JH (2006) Herb-drug interactions in Oncology: Focus on mechanisms of induction. *The Oncologist* 11: 742-752.

Mills E, Cooper C, Seely D, Kanfer I (2005a) African herbal medicines in the treatment of HIV: *Hypoxis* and *Sutherlandia*. An overview of evidence and pharmacology. *Nutr J* 4: 19.

Mills E, Foster BC, van Heeswijk R, Phillips E, Wilson K, Leonard B, Kosuge K, Kanfer I (2005b) Impact of African herbal medicines on

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

antiretroviral metabolism. *AIDS* 19: 95-97.

Moore LB, Goodwin B, Jones SA, Wisely GB, Serabjit-Singh CJ, Willson TM, Collins JL, Kliewer SA (2000) St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc Natl Acad Sci USA* 97: 7500–7502.

Mu Y, Zhang J, Zhang S, Zhou HH, Toma D, Ren S, Huang L, Yaramus M, Baum A, Venkataramanan R, Xie W (2006) Traditional Chinese medicines Wu Wei Zi (*Schisandra chinensis* Baill) and Gan Cao (*Glycyrrhiza uralensis* Fisch) activate pregnane X receptor and increase warfarin clearance in rats. *J Pharmacol Exp Ther* 316: 1369-1377.

Nallani SC, Goodwin B, Maglich JM, Buckley DJ, Buckley AR, Desai PB. (2003) Induction of cytochrome P450 3A by paclitaxel in mice: pivotal role of the nuclear xenobiotic receptor, pregnane X receptor. *Drug Metab Dispos* 31: 681-684.

Nallani SC, Goodwin B, Buckley AR, Buckley DJ, Desai PB (2004) Differences in the induction of cytochrome P450 3A4 by taxane anticancer drugs, docetaxel and paclitaxel, assessed employing primary human hepatocytes. *Cancer Chemother Pharmacol.* 54: 219-229.

Nebel A, Schneider BJ, Baker RK, Kroll DJ (1999) Potential metabolic interaction between St. John's wort and theophylline. *Ann Pharmacother* 33: 502.

Pal D, Mitra AK (2006) MDR- and CYP3A4- mediated drug-herbal interactions. *Life Sci* 78: 2131-2145.

Pichard L, Domergue J, Fourtanier G, Koch P, Schran HF, Maurel P (1996) Metabolism of the new immunosuppressor cyclosporin G by human liver cytochromes P450. *Biochem Pharmacol* 51: 591-598.

Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J (2000) Indinavir concentrations and St John's wort. *Lancet* 355: 547–548.

Ricketts ML, Boekschoten MV, Kreeft AJ, Hooiveld GJ, Moen CJ, Müller M, Frants RR, Kasanmoentalib S, Post SM, Princen HM, Porter JG, Katan MB, Hofker MH, Moore DD (2007) The cholesterol-raising factor from coffee beans, cafestol, as an agonist ligand for the farnesoid and pregnane X receptors. *Mol Endocrinol* 21: 1603–1616.

Rühl R, Sczech R, Landes N, Pfluger P, Kluth D, Schweigert FJ (2004) Carotenoids and their metabolites are naturally occurring activators of gene expression via the pregnane X receptor. *Eur J Nutr* 3: 692–703.

Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G (2000) Acute heart transplant rejection due to Saint John's wort. *Lancet* 355: 548–549.

Saini SP, Mu Y, Gong H, Toma D, Uppal H, Ren S, Li S, Poloyac SM, Xie W (2005) Dual role of orphan nuclear receptor pregnane X receptor in bilirubin detoxification in mice. *Hepatology* 4: 497-505.

Saradhi M, Sengupta A, Mukhopadhyay G, Tyagi RK (2005) Pregnane and Xenobiotic Receptor (PXR) resides predominantly in the nuclear compartment of the interphase cell and associates with the condensed chromosomes during mitosis. *Biochim Biophys Acta -Mol Cell Res* 1746: 85-94.

Saradhi M, Kumar N, Reddy RC and Tyagi RK (2006) Pregnane and Xenobiotic Receptor (PXR): a promiscuous xensosensor with a role in human health and disease. *J Endocrinol Reprod* 10: 1-12.

Seamon KB, Padgett W, Daly JW (1981) Forskolin: unique diterpene activator of adenylate cyclase in membranes and in intact cells. *Proc Natl Acad Sci USA* 78: 3363-3367.

Sidhu JS, Omiecinski CJ (1996) Forskolin-mediated induction of CYP3A1 mRNA expression in primary rat hepatocytes is independent of elevated intracellular cyclic AMP. *J Pharmacol Exp Ther* 276: 238-245.

Singh V, Kaul S, Chanander R, Kapoor NK (1990) Stimulation of low density lipoprotein receptor activity in liver membrane of guggulsterone treated rats. *Pharmacol Res* 22: 37-44.

Stahl W, Schwarz W, Sundquist AR, Sies H (1992) Cis–trans isomers of lycopene and beta-carotene in human serum and tissues. *Arch Biochem Biophys* 294: 173– 177.

Document Produced by deskPDF Unregistered :: http://www.docudesk.com

Staudinger JL, Goodwin B, Jones SA, Hawkins-Brown D, Mackenzie KI, LaTour A, Liu Y, Klaasen CD, Brown KK, Reinhard J, Willson TM, Koller BH, Kliewer SA (2001) The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. *Proc Natl Acad Sci USA* 98: 3369–3374.

Staudinger JL, Ding X, Lichti K (2006) Pregnane X receptor and natural products: Beyond drug-drug interactions. *Expert Opin Drug Metab Toxicol* 2: 847-857.

Synold TW, Dussault I, Forman BM. (2001) The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. *Nature Med* 7:584-590.

Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, Moore DD (2002) A natural product that lowers cholesterol as an antagonist ligand for FXR. *Science* 296: 1703-1706.

van Agtmael MA, Eggelte TA, van Boxtel CJ (1999) Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends Pharmacol Sci* 20: 199-205.

Venkataramanan R, Komoroski B, Strom S (2006) *In vitro* and *in vivo* assessment of herb drug interactions. *Life Sci* 78: 2105-2115.

Wang L, Lee YK, Bundman D, Han Y, Thevananther S, Kim CS, Chua SS, Wei P, Heyman RA, Karin M, Moore DD (2002) Redundant pathways for negative feedback regulation of bile acid production. *Dev Cell* 2: 721–731.

Wentworth JM, Agostini M, Love J, Schwabe JW, Chatterjee VK (2000) St. John's wort, a herbal antidepressant, activates the steroid X receptor. *J Endocrinol* 166: R11-R16.

WHO (2002) Traditional Medicine Strategy 2002-2005, Document WHO/EDM/TRM/2002.1, WHO, Geneva.

Document Produced by deskPDF Unregistered :: http://www.docudesk.com