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Pharmacovigilance: Effects of herbal components on human drugs interactions involving Cytochrome P450

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received November 9, 2008; accepted December 1, 2008; published December 31, 2008

Abstract:
Cytochrome P450 (CYP P450) enzymes are a superfamily of mono-oxygenases that are found in all kingdoms of life. The CYP P450 enzymes constitute a large superfamily of haem-thiolate proteins involved in the metabolism of a wide variety of both exogenous and endogenous compounds. The CYP activities have been shown to be involved in numerous interactions especially between drugs and herbal constituents. The majority of serious cases of drug interactions are as a result of the interference of the metabolic clearance of one drug by yet another co-administered drug, food or natural product. Gaining mechanistic knowledge towards such interactions has been accepted as an approach to avoid adverse reactions. The inductions and inhibition of CYP enzymes by natural products in the presence of a prescribed drug has led to adverse effects. Herbal medicines such as St. John's wort (*Hypericum perforatum*), garlic (*Allium sativa*), piperine (from *Piper* sp.), ginseng (*Ginseng* sp.), gingko (*Gingko biloba*), soya beans (*Glycine max*), alfalfa (*Medicago sativa*) and grape fruit juice show clinical interactions when co-administered with medicines. This review documents the involvement of CYP enzymes in the metabolism of known available drugs and herbal products. We also document the interactions between herbal constituents & CYP enzymes showing potential drug-herb interactions. Data on CYP450 enzymes in activation (*i.e.* induction or inhibition) with natural constituents is also reviewed.

Keywords: Cytochrome P450; CYP; Herb-drug interactions; inhibition; induction; natural products; natural ingredients; phytomolecules

Background:
The name Cytochrome P450 derives from the fact that these proteins have a haem group, and an unusual absorption spectrum range. The reason for cytochrome P450 to absorb in this range is due to the unusual ligand haem iron. Four ligands are provided by nitrogen on the haem ring. The CYP enzymes are a superfamily of haem containing enzymes. In humans, CYP enzymes are important in the production of compounds such as cholesterol, corticosteroids and fatty acids. The most important feature of the CYP enzymes is its unique ability to activate molecular oxygen and to subsequently insert a single oxygen atom stereo-specifically into inert chemical bonds. CYP enzymes catalyses the insertion of oxygen into activated carbon – hydrogen bonds to yield alcohol (e.g. $RH + O_2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$). However, they can also carry out plethora of other reactions including epoxidation, dealkylation and heteroatom oxidation **[1]**. The majority of serious cases of drug interactions are as a result of the interference of the metabolic clearance of one drug by yet another co-administered drug, food or natural product. Gaining mechanistic knowledge towards such interactions has been accepted as an approach, for avoiding adverse reactions. The CYP P450 enzymes, which interact with a plethora of drugs available in the market, have been associated with a majority of the metabolism-related drug-drug interactions known to date **[2, 3]**. It is not surprising that much of the CYP in human is found in the liver, the main organ for drug and toxin removal. However, a significant amount is also found in the small intestine. There are over a thousand different types of CYP known till date. Nevertheless, the number of CYP types in human is relatively less.

The P450 proteins are categorized into families and subfamilies using sequence similarity. Sequences that are greater than 40% identity are considered within a family. Sequences that are greater than 55% identity are considered within a super-family. Humans have 57 CYP genes and more than 59 pseudo-genes divided among 18 families of CYP P450 genes and 43 subfamilies. The summary of the genes and proteins encoded is given in **Table 1** (supplementary material). Several of them have been identified as particularly important in oxidative metabolism. They are CYP3A4 (by far the most important), CYP2D6, CYP2C9, and CYP2C19. Other notable CYPs are CYP2E1, CYP2A6 and CYP1A2.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 3(5): 198-204 (2008)

Enzyme induction occurs for CYP with appropriate substrates. The activity of CYP oxidases do vary across population due to polymorphism. Such differences in activity have clinical consequences, especially when multiple drugs are co-administered.

Biological description of cytochrome P450

The CYP enzymes involved in drug metabolism in humans are expressed predominantly in the liver. However, it is also present in large and small intestines, lungs and brain. They are insoluble proteins bound to the endoplasmic reticulum, with complex mechanistic and structural features. However, the first crystal structures of mammalian CYP enzymes have recently been determined, namely CYP2C5, CYP2B4, CYP2C9 and CYP3A4 **[4, 5]** and thus, much progress can be expected in this area in near future. It is believed that 15-20 different CYP enzyme isoforms contribute to drug metabolism in the human liver. However, the CYP enzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 are considered most important among them **[1, 2, 6]**. These have different yet complementary substrate specificities with ability to metabolize a vast array of xenobiotics. CYP3A4 acts on most lipophilic substrates and is known to metabolize >50% of the drugs in the liver **[7]**, whilst CYP2D6 exhibits a preference for positively charged molecules, usually with a basic nitrogen. CYP2C9 metabolizes weakly anionic molecules, CYP1A2 uses poly-aromatic hydrocarbons and CYP2E1 uses small and soluble organics. Therefore, the CYP system can metabolize almost any organic xenobiotic **[7, 8]**. Most drugs are cleared by CYP proteins. Drugs can increase or decrease the activity of one or more CYP enzymes, which alters the rate at which the drug is degraded and cleared from the body. This can work both ways. When a drug increases the activity of a CYP protein, CYP can render the drug ineffective, because it is cleared too quickly from the body. Alternatively, when a drug inhibits a CYP protein, CYP may not prevent the drug from accumulating to toxic levels, even to the extent of causing an overdose. CYP1, CYP2, CYP3 and CYP4 are the most important for drug biotransformation among CYP proteins and CYP3A4 is the most prevalent CYP in the body and is known metabolise several drugs **[9, 10, 11]**.

Metabolism based interactions

The most common form of drug interactions entail a foreign chemical acting either as an inhibitor or an inducer of the CYP enzyme isoform responsible for metabolizing an administered medicinal drug, subsequently leading to an unusually slow or fast clearance of the drug. More rarely, enzyme stimulation can occur where direct addition of one compound enhances the rate of reaction for substrate **[3]**. Inhibition of drug metabolism will result in an elevation of its concentration in tissues. This leads to various adverse reactions, particularly for drugs with a low therapeutic index. Constant research in this field has been successfully kept updated by developing web based databases for reported and likely drug candidate interactions. The induction of a CYP enzyme isoform responsible for the metabolism of a drug can reduce its expected therapeutic capacity due to depletion of its plasma concentration. A higher dose of the parent drug is therefore required for effective therapy, with further dosage tailoring as and when the inducer effects are withdrawn. This is true in many instances. It should be note that CYP enzyme induction rarely leads to toxicity, except in cases where the metabolite is particularly harmful. For example, CYP1A1 and 1A2 have been implicated in increased carcinogenic activation of chemicals. Thus they are considered as a potential risk factor in certain cancers and hence drugs that induce these reactions are preferentially avoided by the pharmaceutical industry **[10, 12]**. Several popular herbs have been reported to participate in interactions with medicinal drugs leading to clinically relevant drug adversities. A few examples that involve CYP enzymes and are highlighted in this review along with predicted as well as experimental interactions are summarized in **Table 2** (supplementary material). A few examples of herbal constituents and drugs that interact with human CYP enzymes are highlighted in **Table 3** (see supplementary material).

Hypeforin from St. John's Wort herb (*Hypericum perforatum*)

A popular herb largely used in the treatment of depression is St. John's Wort (SJW). It has been implicated with a number of clinically significant interactions with medicinal drugs, one of the more potentially fatal being with cyclosporine. Cyclosporine is an immunosuppressant with a narrow therapeutic index administered to transplant patients. In reported cases, consumption of various levels of SJW (from 300 mg/day for 4 weeks to 2 or 3 × 300 mg/day for 6 months) lead to a decrease in cyclosporine levels below the desirable effective therapeutic range of 200-350 µg/L causing cellular rejection of the tissue **[13]**. The induction of CYP3A4 through the activation of pregnane X-receptor by both the crude extract and hyperforin (one of the active ingredients) has been demonstrated in primary human hepatocyte cultures. In addition, the induction of intestinal multidrug resistant transporter protein MDR1/P-glycoprotein has been demonstrated in clinical and preclinical (rat *in vivo*) investigations **[14, 15]**. Results of these studies explain the combined increase in absorption and metabolism of drugs such as cyclosporine in the presence of SJW, thus resulting in a severe decrease in the serum availability of the drug leading to declined therapy. They also provide a mechanism-based explanation for other SJW-mediated adversities in the presence of prescription medicines whose metabolism is catalyzed by CYP3A4. Such instances include the loss of anticoagulant activity of warfarin and the intermenstrual bleeding in several females on the contraceptive, ethinylestradiol **[16, 17]**. A recent clinical study examining the metabolism of omeprazole has established that in addition to the induction of CYP3A4, SJW enormously decreases the plasma concentration of the drug through the induction of CYP2C19, which is responsible for the hydroxylation of the drug **[18]**.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 3(5): 198-204 (2008)

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Allicin from Garlic (Allium sativum)

Garlic is used for the reduction of hypertension and hyperlipidaemia. It has been implicated in the decrease of the plasma concentration of protease inhibitor saquinavir **[19, 20]**. The induction of gut CYP3A4 by garlic was thought to be a plausible explanation for the reduction in bioavailability of the drug known to be primarily metabolized by CYP3A4 **[21]**. The active ingredient allicin has also shown potent inhibitory activity on CYP2C9 and 2C19. The potential drug adversities predicted for each of these active ingredients as a result of their interactions with CYP enzymes has to be examined in a clinical setting to know the extent to which garlic can interact with co-medications **[20, 22]**.

Piperine from Piper (Piper nigrum)

In clinical trials, piperine has shown to increase the bioavailability of phenytoin, propranolol and theophylline **[23]**. Although *in vivo* study on rat has demonstrated that piperine treatment suppressed CYP2E1 expression and enhanced 2B and 1A expression **[12, 24]**. It should be noted that the clinical observations are due for CYP isoforms for further research.

Ginsenoside from Ginseng (Panax ginseng)

Ginseng (*Panax ginseng*) has been shown to induce mania when used concomitantly with phenelzine **[25]**. Bipolar disorder (mania) also known as manic depression (or bipolar depression) and is a common mood disorder that affects about 5.7 million Americans (www.medicinenet.com/bipolar_disorder/article.htm). *In vitro* studies using both crude ginseng extract and total saponins at high concentrations (>2000 µg/mL) showed the inhibition of CYP2E1 activity in mouse and human microsomes **[26]**. Ginsenoside caused weak inhibitory activity against CYP3A4, CYP2D6, CYP2C19 and CYP2C9 while ginsenoide increased the activity of CYP2C9 and CYP3A4 **[26, 27]**. The effect of this herb and its ingredients on CYP enzymes is yet to be substantiated in an *in vivo* context.

Ginkgolic acid from Gingko (Gingko biloba)

In vitro and *in vivo* analysis carried out on hepatic and intestinal CYP enzymes of rat, have demonstrated that the leaf extract inhibits the metabolism of diltiazem, which is a typical substrate for CYP3A **[28]** and also induces CYP2B enzymes **[29]**. In addition, ginkgolic acids were shown to be potent inhibitors of CYP1A2, CYP2C9 and CYP2C19 under CYP enzymes case study **[30]**. Although flavanol aglycones showed significant inhibitory activity against CYP1A2, 2C9 and 3A, recent findings showed that the most abundant components of gingko preparations in clinical use (terpene trilactones and flavanol glycosides) do not significantly inhibit major CYP enzymes in microsomes of human's liver **[16, 22, 29]**. The variations of constituents of gingko (ginkgolides, biobalides, and flavone glycosides) and their bioavailabilities could explain the disparity in findings, in addition to species variability in drug metabolism.

Pharmacovigilance

The under-reporting of adverse drug reactions in developing countries including India, Sri Lanka and the Philippines **[31]**, is possibly the main reason why only 3% of the adverse drug reactions reported in the WHO database have been added from the developing countries where approximately 80% of the world's population lives. In these countries, a strong practice of traditional medicine exists and adverse drug reactions go unrecognized as part of the healing process. There is generally a misconception that natural therapies are safe. The reluctance of physicians trained in Western medicine to give recognition to these traditional practices also leads to a lack of acknowledgement of possible drug-herb interactions **[32]**. The world consumption of natural products for medicinal purposes is immense. According to WHO estimates, 30-50% of total medicinal consumption in China can be accounted by herbal preparations, 70% of Canadians and >50% of Europeans, North Americans and persons living in other industrialized regions have used complementary medicine at least once, in addition to the high incidence of practice in Africa, Latin America and Asia **[8, 33, 34]**.

Future prospects:

The role of metabolism in drug-herb components interactions and in turn the role of CYP enzymes in such interactions cannot be overstated. Studies that could establish the various phenotypes and genotypes of CYP alleles for populations in various ethnic groups, the impact of environmental, dietary and social habits on CYP activity, the metabolism of natural products by CYP enzymes and the impact of these natural products on the CYP enzyme activities would allow initial predictions. Hence, prevention of likely adverse drug reactions involving these crucial enzymes is possible. Gaining a mechanism based understanding lies at the root of avoiding these enzyme-related drug adversities. Cytochrome P450 is an ideal target for these studies. The ability to make such predictions would be of enormous benefit to pharmacogenomics studies as P450 plays a vital role in the metabolism of drugs. The Cytochrome is of special interest in pharmacology as it is responsible for the metabolism of many pharmacologically active molecules. The use of *in silico* protein–drug interactions studies and computer aided drug designing approach and quantum mechanical calculations will allowing to know the mechanism of interaction of P450 with herbal constituents. This in turn will allow theories regarding unknown features of human P450 to be tested and predictions to be made for the result of an interaction of herbal constituents within a given P450. The computational approaches could be used to analyze the interactions, regarding the processes on such binding which helps to predict new conformations of active site. The introduction of some of the determined contact residues of the active site into the model will allow the orientation of herbal constituents and lead molecules.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 3(5): 198-204 (2008)

Acknowledgment:
We acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi and Department of Biotechnology (DBT), New Delhi for financial supports to the Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow (UP), INDIA.

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Edited by P. Kangueane
Citation: Saxena *et al.*, Bioinformation 3(5): 198-204 (2008)

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 3(5): 198-204 (2008)

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Supplementary material

CYP family	Function	Category	CYP Isoform
CYP1	Drug and steroid (especially estrogen) metabolism	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1 CYP1A2 CYP1B1
CYP2	Drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6 CYP2A7 CYP2A13 CYP2B6 CYP2C8 CYP2C9 CYP2C18 CYP2C19 CYP2D6 CYP2E1 CYP2F1 CYP2J2 CYP2R1 CYP2S1 CYP2U1 CYP2W1
CYP3	Drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4 CYP3A5 CYP3A7 CYP3A43
CYP4	Arachidonic acid or fatty acid metabolism	6 subfamilies, 11 genes, 10 pseudogenes	CYP4A11 CYP4A22 CYP4B1 CYP4F2 CYP4F3 CYP4F8 CYP4F11 CYP4F12 CYP4F22 CYP4V2 CYP4X1 CYP4Z1
CYP5	Thromboxane A2 synthase	1 subfamily, 1 gene	CYP5A1
CYP7	Bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1 CYP7B1
CYP8	Varied	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)
CYP11	Steroid biosynthesis	2 subfamilies, 3 genes	CYP11A1 CYP11B1 CYP11B2
CYP17	Steroid biosynthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1
CYP19	Steroid biosynthesis: aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1
CYP20	Unknown function	1 subfamily, 1 gene	CYP20A1
CYP21	Steroid biosynthesis	2 subfamilies, 2 genes, 1 pseudogene	CYP21A2
CYP24	Vitamin d degradation	1 subfamily, 1 gene	CYP24A1
CYP26	Retinoic acid hydroxylase	3 Subfamilies, 3 genes	CYP26A1 CYP26B1 CYP26C1

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CYP27	Varied	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D3 1-alpha hydroxylase, activates vitamin D3) CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1
CYP46	Cholesterol 24-hydroxylase	1 subfamily, 1 gene	CYP46A1
CYP51	Cholesterol biosynthesis	1 subfamily, 1 gene, 3 pseudogenes	CYP51A1 (lanosterol 14-alpha demethylase)

Table 1: Classification of the CYP family on the basis of CYP isoform and function is given.

S. No.	Name of medicinal plant	Herbal component and Chemical formula	IUPAC name	PubChem CID*
1.	St.John's wort (*Hypericum perforatum*)	Hyperforin $C_{35}H_{52}O_4$	4-Hydroxy-5-isobutyryl-6-methyl-1,3,7-tris-(3-methyl-but-2-enyl)-6-(4-methyl-pent-3-enyl)-bicyclo[3.3.1]non-3-ene-2,9-dione	5288591
2.	Garlic (*Allium sativum*)	Allicin $C_6H_{10}OS_2$	3-prop-2-enylsulfinylsulfanylprop-1-ene	65036
3.	Piperine (*Piper nigrum*)	Piperine $C_{17}H_{19}NO_3$	(2E,4E)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one	638024
4.	Ginseng (*Panax ginseng*)	Ginsenoside $C_{30}H_{52}O_2$	(3S,5R,8R,9R,10R,14R,17S)-17-(2-hydroxy-6-methylhept-5-en-2-yl)-4,4,8,10,14-pentamethyl-2,3,5,6,7,9,11,12,13,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	3086007
5.	Gingko (*Ginkgo biloba*)	Ginkgolic acid $C_{22}H_{34}O_3$	2-hydroxy-6-[(Z)-pentadec-8-enyl]benzoic acid	5281858

Table 2: Medicinal plants with their herbal components, IUPAC name, Chemical structure and PubChem CID number. (Note: * = PubChem compound identity descriptor number (http://pubchem.ncbi.nlm.nih.gov/)).

S. No.	Medicinal plant	Herbal constituent and chemical formula	Drug	Experimental model	CYP enzyme involved (isoform)	Symptom of interaction	Mechanism
1.	St. John's wort (*Hypericum perforatum*)	Hyperforin $C_{35}H_{52}O_4$	Ciclosporin	Human hepatocytes	CYP3A4, 2E1, 2C19	Reduction in serum	Induction of p-glycoprotein
2.	St. John's wort (*Hypericum perforatum*)	Hyperforin $C_{35}H_{52}O_4$	Warfarn	Human clinical trail	CYP3A4	Loss of anticoagulant activity	Inhibition of CYP activity
3.	St. John's wort (*Hypericum perforatum*)	Hyperforin $C_{35}H_{52}O_4$	Omeprazole	Human clinical trail	CYP2C19	Decreases Plasma concentration	Induction of CYP2C19 , 3A4
4.	Garlic (*Allium sativum*)	Allicin $C_6H_{10}OS_2$	Sequinavir	Human clinical trail	CYP3A4	Reduction of hypertension	Inhibition of CYP2C9, 2C19, 3A4
5.	Garlic (*Allium sativum*)	Allicin $C_6H_{10}OS_2$	Sequinavir	Human clinical trail	CYP2C9, 2C19	Reduction of hypertension and hyperlipidameia	Inhibition of CYP2C9, 2C19

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6.	Black Pepper (*Piper nigrum*)	Piperine $C_{17}H_{19}NO_3$	Antimicrobial	*In vivo* studies in rat	CYP2E1	suppressed CYP2E1 expression	Induce activity of CYP 1A , 2B
7.	Ginseng (*Panax ginseng*)	Ginsenoside $C_{42}H_{72}O_{14}$, Ginsenoide	Phenelzine	*In vitro* studies in mouse and human microsomes	CYP2E1	Induce CYP3A4, 2D6, 2C19 , 2C9 activity	Inhibition of CYP2E1 activity
8.	Gingko (*Gingko biloba*)	Ginkgolic acid $C_{22}H_{34}O_3$	Diltiazem	*In vitro* and *in vivo* analysis on rat hepatic and intestinal CYP enzymes	CYP3A, 2B	Inhibit metabolism of Diltiazem (drug)	Induces CYP2B and inhibit CYP1A2, C9 2C19

Table 3: Assessment of herbal components on drug interactions and effects on CYP activities

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 3(5): 198-204 (2008)