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Review Article

A Scientific Insight into Step by Step Procedures for the Prediction of Cytochrome Enzyme Oriented Herb-Drug Interactions

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ABSTRACT:
Background: Herbs are widely used by majority of the patient for their chronic illness at least once in their life time. Liver enzymes play a major role in the metabolism of xenobiotics. In vivo & In vitro technique prediction of drug interaction is widely practiced.
Method: Since there is no standard database for the prediction of herb-drug interaction. Abroad literature survey is carried out to ensure the process of prediction of herb-drug interaction from the various databases. For the prediction of herb-drug interaction step by step, strategy is enumerated in this review.
Discussion: The drug interaction potential of targeted drug estimated by in silico, in vitro, in vivo animal model and phase one trial. CYP450 enzyme inhibition potential was assessed using High throughput screening assay followed by drug binding affinities measured through in silico studies.
Conclusion: This study gives the step-by-step approach to analyzing the drug interaction potential herbal medicine with CYP450 enzymes.

Keywords: CYP450, Healthy volunteers, Herb-drug interaction, In vivo, In vitro, In silico, Probe drug.

1. INTRODUCTION

Complementary and alternative medicines trends have been increased gradually throughout the world. Alternative medicines (Herbal, Ayurvedic, Siddha, Unani etc.,) are widely used by majority of the patients for their chronic illness at least once in their life time. Since all the alternative therapies are generated from ancient techniques, people believe that herbs are inherently safe and they are self-prescribed. The patient chooses herbal medicine due to the discomfort of existing conventional therapy, like not an improvement in symptoms, cost-effective, repeated hospitalization and side-effects [1-4]. Patients with chronic disease concomitantly administered with traditional medicine and herbal medicine. Around 60% of the herbal medicine users do not disclose their herbal use with their treating physician. All the xenobiotics are metabolized in the liver by CYP450 enzymes. Were CYP3A4 plays a major role in the metabolism of 65% of conventional drugs. As per the existing data, the herbs are metabolized by CYP450 enzymes [5-9]. Our study hypothesis, when the polyherbal formulation or herbal product is administered with conventional medicine. The polyherbal formulation may alter the CYP450 enzymes, which may lead to either drug toxicity or therapeutic failure of the targeted drug since there is no single robust methodology to estimate the drug interaction potential of herbal medicines. This review aims to give the step by step methods to predict the drug interaction potential of herbal medicines.

2. NEED OF STUDY

WHO estimates that not less than 80% world population uses herbal medicine for some aspects of primary health care. Drug interaction has been the 4th or 6th cause of death. More than 70 to 80 herbs increase the risk of bleeding. More than 30 to 40 herbs like ephedra (54 deaths, 1600 adverse events) show the possibility of causing hepatic failure. More than 60% of Asians resort to herbal products to treat a variety of chronic disorders such as anxiety, depression, dementia and memory impairment, headache, weight loss etc. About one in three concurrent users were at risk of a potential herb-drug or supplement-drug interaction. Most of the HDI studies so far are very limited and specific to a few conventional drugs and herbal drugs.

3. METHOD

This study describes the step by step approaches to estimate the cytochrome mediated drug interaction [Table 1].

Table 1: Methodologies to follow determine drug interaction potential

S.NO	Procedures	Expected outcome
1.	Standardization of herbal product	Quantification of phyto compounds
2.	Method development and validation of probe drug.	Accuracy, precision, LOD, LOQ, retention time prediction, peak determination.
3.	Administration of investigational drug in animal model (*In vivo* procedure)	Safety and efficacy of a targeted can be analyzed followed by Estimation of pharmacokinetic parameters.
4.	High throughput screening assay	Ensures the enzyme CYP450 Enzyme concentration.
5.	*In silico* studies	In silico model is expressed to predict the targeted molecule with specific enzyme.
6.	Administration of investigational drug in healthy adult volunteers (phase 1 trial)	Clinical evidence ensures the pharmacokinetic profile of a drug. The interaction potential can be easily differentiated with control group and treatment group.

3.1 Need for standardization of herbal product:

Herbs are widely used by the majority of patient for various illness. The challenge in the prediction of herb-drug interactions is that a single herbal plant contains numerous phytochemical compounds. For example, A single *Commiphora mukkul* plant contains E-Guggulsterone, Z-guggulsterone, E-Guggul sterol, Z-Guggulsterol, myrcene, eugenol, Quercetin, gallic acid, ellagic acid etc [10]. In this condition, it is very difficult to predict the causative agent. To ensure the main drug interaction potential, the major bioactive compound should be verified.

3.2. Selection of probe drug:

Probe drug is a small molecule and a kind of bio-marker (Target tractability) widely used for the prediction of herb-drug interaction. There are approximately 60 isoenzymes identified, and the selection probe drug is based on targeted enzyme-like CYP3A4, CYP2D6 AND CYP2C19 etc. The list of probe drugs is mentioned in table 2.

Table 2: List of probe drugs

CYP3A4	CYP2D6	CYP2C19
Alfentanil	Atomoxetine	S-mephenytoin
Avanafil	Desipramine	Omeprazole
Buspirone	Dextromethorphan	Diazepam
Conivaptan	Eliglustat	Lansoprazole
Lovastatin	Nebivolol	Rabeprazole
Midazolam	Nortriptyline	voriconazole
Saquinavir	Perphenazine	S-mephenytoin
Simvastatin	Tolterodine	
Sirolimus	R-venlafaxine	
Tacrolimus		
Vardenafil		

3.3 Administration of the investigational drug in the animal model (*In-vivo* procedure)

In history from the antiquated period, Animal models are utilized as a source of perspective of human life structures and physiology. Animal simulation gives the exact pharmacological and therapeutic response of drugs and new chemical entities. Animal models can be carried out by two different groups where one group is the control (treated placebo), and another group is treated with the investigational drug. The outcome of pharmacokinetic parameters can be compared through the control and treatment group.

3.4. High throughput screening assay (HTS):

HTS assay is used to ensure the presence of CYP450 enzymes as well the protein concentration, inhibition potential of the herbal formulation by means of comparing with standards and positive control.

3.5. *In silico* studies:

Computer-aided techniques are used to assess whether the Compounds were designed to obey Lipinski's Rule of Five followed by binding model & binding affinity. *In silico* studies involve molecular docking and assessment of ADMET, OSIRIS, T.E.S.T, ProTox- II, MOLINSIPIRATION, Swiss Target Prediction parameters. In silico represents the computer-aided relatively interaction potential between the targeted molecule and how a drug interacts with CYP450 enzymes by means of comparing with standard positive control.

3.6. Administration of the investigational drug in healthy adult human volunteers (phase one clinical trial):

To ensure the safety and efficacy of a targeted compound, clinical studies are conducted in healthy volunteers. The outcome can be estimated through the pharmacokinetic result of the targeted drug.

4. DISCUSSION

This qualitative review gives a step by step methodology to predict the herb-drug interaction. Over 65% of conventional medicines are metabolized in phase one pathway by the CYP3A4 isoenzyme. Standardization of herbal product can be determined by HPTLC techniques by comparing the peak with standards. A study reported the presence of E, Z Guggulsterone in the marketed polyherbal formulation. [10] The probe drug method is widely practised to assess the drug interaction. Even though lots of substrates reported Midazolam, Dextromethorphan and omeprazole are used as a sensitive probe for CYP3A4, CYP2D6 AND CYP2C19, respectively. From the existing data, midazolam is reported as a sensitive and suitable probe for CYP3A4 isoenzyme. To use the probe drug technique, the selected probe drug has to developed and validated for accuracy, precision, run time, peak, LOD and LOQ etc., by the HPLC method [11, 12]. *In vivo* model gives the pharmacokinetic alteration of the investigational drug. The drug interaction potential is measured by comparing the pharmacokinetic parameters of the probe drug in the control group and treatment group. The *in vivo* studies ensure the inhibition/induction potential of herbs [13-17]. Prediction of drug interaction from *In vitro* studies has become a rapidly expanding field of research in

recent years [18, 19]. Molecular docking analysis gives crystal-clear data of targeted compound based on the nature of the chemical. The ADMET prediction of targeted can be measured by the introduction of chemical smiles in the admetSAR (version2) online database. The online database gives absorption, Distribution, metabolism, excretion, toxicity and CYP inhibitor category. Based on the binding energy of the object drug and positive control, the interaction potential is estimated [20-22]. Clinical evidence is used to assess the safety and efficacy and also the inhibition/induction potential of herbal medicine. Evidence from the healthy volunteers, it gives a clear understanding of the pharmacokinetic parameters of the investigational drug [23-25]. The pharmacokinetic parameters such as drug concentration, t1/2, T_{max}, Mean residence Time and clearance. In healthy volunteers gives significant changes when compared with sick patients [26-30]. The drug interaction is often reported in a patient with multiple prescribers, polypharmacy, genetic polymorphism, special category populations patients with existing illness like liver disease and renal failure.

5. CONCLUSION

We have observed that most of the herbal medicines tend to inhibit/induce CYP450 enzymes and may lead to drug toxicity or therapeutic failure. However, there is no specific standard database to report the herb-drug interactions in advance completely. This study gives the step by step approach to analyzing the drug interaction potential of herbal medicines with CYP450 enzymes. By selecting the appropriate method in a distinguished manner, a CYP450 enzyme-mediated drug interaction can be predicted easily.

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