

Mechanisms and Implication of Drug-Herbal Interactions

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It has been well recognized that an increasing percentage of the population is using herbal products for both preventive and therapeutic purposes. Often times the use of herbals is associated with attenuating side-effects produced from therapeutic drugs such as chemotherapeutic regimen. The basis of this usage of herbal products is the concept that being a natural product, the herbal must be safe to use. However, contrary to this perception it has been well documented that significant pharmacokinetic and/or pharmacodynamic effects can occur through herb-drug interaction [1,2] which has led to an increased concern regarding the safety and even toxicity of the co-administration of these products with therapeutic drugs [3-7]. This effect is exacerbated more so for drugs that have a narrow therapeutic index (e.g., warfarin, digoxin, and many chemotherapeutic agents). The mechanisms of herbal-drug interaction are generally pharmacokinetic in nature and result in changes in absorption and metabolism of the therapeutic agent. In addition to the chemical/physical properties of drugs that effect absorption after oral dosing (e.g., lipid/water solubility, molecular size, degree of ionization, etc), the inhibition or induction of drug transporters can have a substantial effect on the amount of drug absorbed. Perhaps the best characterized drug transporter is P-glycoprotein (P-gp) which has been found in the apical membrane of cells in various organs including the gastrointestinal tract, liver, lungs, and kidneys. Active compounds in the herbal product have been shown to function as transporter substrates resulting in either inhibition or induction of P-gp causing either elevated or reduced drug concentrations, respectively [7,8]. These alterations in drug concentration could result in either a sub-therapeutic level of exposure or potentially produce toxic side effects.

Herbal products also have components which function as cytochrome P450 (CYP450) substrates which may also result in the inhibition [9] or induction [10] of the metabolizing enzymes. For inhibition of CYP450 enzymes, herbal products do so in a mixed competitive/noncompetitive manner depending on the particular isozyme and active compounds in the product [9,11]. Competitive inhibition is reversible and is usually simple competition between the drug and the active herbal component for the reactive site on the enzyme. Noncompetitive inhibition is typically characterized by reversible binding of the inhibitor at an allosteric site on the enzyme resulting in a change in its conformation where the drug substrate can still bind but the enzyme cannot catalyze the biotransformation of the drug. Additionally, active components of the herbal may bind irreversibly through covalent interactions with the enzyme thereby reducing the concentration of the enzyme. Alternatively, metabolites of the herbal may also bind irreversibly to the enzyme (mechanism based inhibition) again reducing the pool of enzymes available to catalyze biotransformations of the drug. In this case, the subsequent recovery of P450 enzyme activity is completely reliant on de novo synthesis of new proteins and thereby produces a significant delay between withdrawal of the herbal product and recovery of metabolic activity. Reversible inhibition compared with mechanism based inhibition is characterized by a time, concentration and NADPH dependence [11,12].

The induction of CYP450 enzymes by herbal products can also have serious effects on the pharmacokinetics of drugs which could result in increases in drug clearance, bioactivation of prodrugs and in concentration of toxic metabolites. An increase in the clearance of a drug due to higher metabolic activity stemming from the induction of CYP450 enzymes from an herbal product will reduce the therapeutic effect of the drug [5,13-15]. The bioactivation of orally administered prodrugs could significantly increase the systemic levels of the active drug thereby increasing the possibilities of side-effects and toxicity due to increased concentrations of the active form of the drug. Toxic effects could also occur due to elevated levels of toxic metabolites produced as a direct result of enzyme induction.

It has also been noted that herbal products can be co-substrates for both P-gp and CYP450 thereby possessing the potential to produce a combination of the above listed effects. The interdependence of both transport and metabolism can make it difficult to understand the role in the final bioavailability and disposition of a drug when co-administered with an herbal product. This concept combined with the fact that herbal products can vary greatly in the composition of components as a result of different preparations, seasonal variations and geographic location add another degree of complexity to understanding and predicting potential interactions. As a result there is clearly a need to gain a better understanding of potential herbal-drug interactions in order to provide data for safe clinical use.

References

1. Butterweck V, Derendorf H (2008) Potential of pharmacokinetic profiling for detecting herbal interactions with drugs. *Clin Pharmacokinet* 47: 383-397.
2. Tarirai C, Viljoen AM, Hamman JH (2010) Herb-drug pharmacokinetic interactions reviewed. *Expert Opin Drug Metab Toxicol* 6: 1515-1538.
3. Hafner-Blumenstiel V (2011) Herbal drug-drug interaction and adverse drug reactions. *Ther Umsch* 68: 54-57.
4. Skalli S, Zaid A, Soulaymani R (2007) Drug interactions with herbal medicines. *Ther Drug Monit* 29: 679-686.
5. Izzo AA, Ernst E (2001) Interactions between herbal medicines and prescribed drugs: a systematic review *Drugs* 61: 2163-2175.
6. Chavez ML, Jordan MA, Chavez PI (2006) Evidence-based drug-herbal interactions. *Life Sci* 78: 2146-2157.
7. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH (2007) Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). *Oncologist* 12: 927-941.

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Received May 10, 2012; Accepted May 12, 2012; Published May 14, 2012

Citation: Gorman GS (2012) Mechanisms and Implication of Drug-Herbal Interactions. *J Bioequiv Availab* 4: xiii-xiv. doi:10.4172/jbb.10000e16

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8. Brown L, Heyneke O, Brown D, van Wyk JP, Hamman JH (2008) Impact of traditional medicinal plant extracts on antiretroviral drug absorption. *J Ethnopharmacol* 119: 588-592.
9. Obach RS (2000) Inhibition of human cytochrome P450 enzymes by constituents of St John's wort, an herbal preparation used in the treatment of depression. *J Pharmacol Exp Ther* 294: 88-95.
10. Tirona RG, Bailey DG (2006) Herbal product-drug interactions mediated by induction. *Br J Clin Pharmacol* 61: 677-681.
11. Zhou S, Koh HL, Gao Y et al. (2004) Herbal bioactivation: the good, the bad and the ugly. *Life Sci* 74: 935-968.
12. Taesotikul T, Dumrongsakulchai W, Wattanachai N, Navinpipat V, Somanabandhu A, et al. (2011) Inhibitory effects of *Phyllanthus amarus* and its major lignans on human microsomal cytochrome P450 activities: evidence for CYP3A4 mechanism-based inhibition. *Drug Metab Pharmacokinet* 26: 154-161.
13. Kupiec T, Raj V (2005) Fatal seizures due to potential herb-drug interactions with *Ginkgo biloba*. *J Anal Toxicol* 29: 755-758.
14. Yin OQ, Tomlinson B, Waye MM, Chow AH, Chow MS (2004) Pharmacogenetics and herb-drug interactions: experience with *Ginkgo biloba* and omeprazole. *Pharmacogenetics* 14: 841-850.
15. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB (2003) Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* 73: 41-50.