Editorial

Herb-Drug Interactions: Theory *versus* Practice

The goal of this special issue is to clarify some of the more confusing and controversial subjects within the area of herb-drug interactions. The concept that foods and botanical agents, officially classified as over-the-counter dietary supplements, could enhance or reduce the effects of prescribed medications has gained our attention only gradually. But with almost $5 billion in sales in the United States in 2007, herbal dietary supplements are now demanding our utmost attention [1]. The issue of food-drug interactions first became widely known in 1989 when grapefruit was first found to increase the blood levels of felodipine, a calcium channel blocker, and later, in 1996, terfenadine, a non-sedative antihistamine. Subsequent investigations suggested that these effects were due to inhibition of intestinal CYP3A4 and P-gp by naringenin and furanocoumarins, naturally-occurring substances in grapefruit. Terfinadine was removed from the market in 1998 because of its high rate of interactions; inhibition of CYP3A4 led to elevated blood levels, which caused prolonged QT intervals and subsequent cardiac arrhythmias.

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Since reports of St. John's wort (SJW) reducing blood levels of digitalis and cyclosporin in 2000, the number of anecdotal reports of possible herb-drug interaction has increased dramatically. The effects of SJW were magnified by the induction not only of CYP3A4, but also P-glycoprotein (permeability glycoprotein; now called MDR1 or ABCB1). Relatively toxic drugs such as antivirals, chemotherapeutics, and immunosuppressants are often substrates of both CYP3A4 and P-glycoprotein, potentially resulting in significantly decreased blood levels [2]. Unfortunately, the available case reports rarely describe the products actually consumed and have often struck an alarmist tone with titles such as: "Coma from the health food store". Encouraging the use of simple, *in vitro* screening methods for cytochrome P450 enzymes to get some grasp of how significant the problem might be, seemed a rational response. However, the *in vitro* studies that began to appear in the literature often used enormous concentrations of crude extracts or their constituents (from hundreds to thousands of times a realistic plasma level). Some of the components of these extracts would not have been absorbed after oral administration. As a result, the scientific literature has become a reservoir of potentially irrelevant and misleading information about herb-drug interactions. Crying "wolf" too often may have unintended consequences, such as obscuring objective data collection and confusing clinical recommendations. To be useful, a case report must contain certain basic information in addition to temporal relationship and concomitant medications. There must be as much information as possible about the particular product in question, or it would be difficult to determine if a potential interaction was caused by one or more of the ingredients listed on the label, from accidental or intentional adulteration, or from contamination of the product with some toxic plant, heavy metal, or pharmaceutical.

Some of the difficulties in predicting *in vivo* effects from *in vitro* data are discussed by Markowitz *et al*. in this issue (pp. 747 – 754). Occasional clinical pharmacokinetic studies, such as those below by Gurley *et al*. (pp. 755 – 763 and pp. 772 – 779), can bring some reality to the chaos by providing clinical relevance to the theoretical interactions inferred by *in vitro* data. Unfortunately, given the lack of a broad set of qualified data and a clear model for assessing relative impact, patient variability factors, and potential risk, one dramatic case report of a possible interaction all too often will trump a well-controlled human trial with actual kinetic data showing no interaction. The literature "confirms" the case report or the *in vitro* effect by repeating it over and over again in letters, reviews and books while neglecting to critically assess data quality and clinical relevance.

The papers by Freeman and Spelman (pp. 789 – 798) and by Bone (pp. 764 – 771) critically assess the evidence for drug interactions reported for echinacea and ginkgo, respectively. Neustadt and Pieczenik (pp. 780 – 788) provide speculation concerning mechanisms of drug toxicity that might actually be prevented by the judicious application of specific supplements. Finally, Tomlinson *et al*. (pp. 799 – 809) share important insights into the importance of pharmacogenetics for predicting herb-drug interactions in the future.

For a broader scope on food and herb interactions with drugs, the interested reader may wish to refer to an excellent, recent book on this subject [3]. It is hoped that this special issue will stimulate some lively discussions and provide some fresh perspectives, and inspire a new level of thoughtful and responsible discourse for these rapidly evolving fields of therapeutics and of personal health maintenance.

Jerry M. Cott
U.S. Food and Drug Administration, Silver Spring, MD

Conflict of interest statement: The opinions expressed are those of the guest editor and not that of the U.S. Food and Drug Administration or the U.S. Federal government.

[1] Blumenthal, M., Cavaliere, C., Rea, P., Herbal Supplement Sales in Unitrd Staates show growth in all channels. *Herbal-Gram* 2008, *78*, 60 – 63.

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[3] Stargrove, M. B., Treasure, J., McKee, D. L. (Eds.), *Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies*, Elsevier, Mosby 2008.

