This Month in APR

By Dong Hee Na, Associate Editor

Metabolism study of botanical drugs

The article focused in this issue (Song et al., 2010) describes *in vitro* metabolism study of jaceosidin, which is a bioactive flavonoid compound found in the medicinal herbs of *Artemisia* species (Kim et al., 2008). Recently, synthetic approaches to drug discovery have been declined in new drug development, whereas the market of botanical therapeutics such as dietary supplements or botanical drugs is growing and the development has been increasingly received attention. Botanical drug, as defined by the US Food and Drug Administration (FDA), is a drug product that is prepared from one or more plants, algae, or macroscopic fungi by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. Botanical drug products are available in a variety of dosage forms, such as solutions, powders, tablets, capsules, elixirs, and topicals (Goldman, 2001). FDA regulatory management of botanical drugs is the same as non-botanical drug product. However, there are particular circumstances that are taken into consideration: botanical drugs may be prepared as complex mixture, all chemical constituents are not well defined, and the active constituents may not be identified.

Drug metabolism is the conversion of xenobiotics into other compounds and this transformation usually occurs through specialized enzymes. In discovery and development of new drug, drug metabolism study plays an important role in identifying the major metabolites of new chemical entity, ascertaining the major enzymes responsible for the biotransformation of drug, and predicting potential drug-drug interactions and pharmacogenetic idiosyncrasies. The identification of biologically active metabolites actually resulted in the development of more safe and potent drugs, for example, acetaminophen from acetanilide (Brodie and Axelrod, 1948) and fexofenadine from terfenadine (Yun et al., 1993). In the development of botanical drugs, the metabolism study is also very important. A general misconception persists among botanical drug users that botanical drugs are safe and free from side effects and drug interactions because those are of natural origin. However, there are increased numbers of reports on the interaction between botanical drugs such as St. John's wort, garlic, and Ginko biloba and prescribed drugs. Primary mechanisms of herb-drug interactions involve either induction or inhibition of hepatic and intestinal drug-metabolizing enzymes, such as cytochrome P450s (CYPs), UDP-glucuronosyltransferases (UGTs), and drug transporters, such as P-glycoprotein (Venkataramanan et al., 2006; Kober et al., 2008; Ulbricht et al., 2008; Yang et al., 2010). Many botanical compounds undergo the metabolism with CYPs, UGTs and sulfotransferases, and some of their active ingredients are substrates of P-glycoprotein (He et al., 2010). Therefore, pharmacokinetic studies of botanical drugs should address the followings: (i) bioavailability to assess to what degree and how fast they are absorbed after administration, (ii) elucidation of metabolic pathways, (iii) assessment of their elimination routes and kinetics, and (iv) interactions of botanical drugs with synthetically derived drug products.

In the metabolism study, identification of metabolites and elucidation of metabolic pathways are mainly based on the data obtained from *in vitro* incubation study and *in vivo* animal and human trials. *In vitro* metabolism study is efficient and convenient tool because the identification of new metabolites is much easier than *in vivo* systems and screening assay using highly purified metabolizing enzymes and their inhibitors can generate information on potential metabolic routes (Venkatakrishnan et al., 2003; Chen et al., 2007). In general, the *in vitro* metabolism study of botanical drug can address (i) assessment of quantitative content of main components, (ii) identification of components that can be absorbed from gastrointestinal tract, (iii) metabolic stability, metabolic profile and characterization of metabolic enzymes in gastrointestinal tract (intestinal bacteria, acid, or intestinal metabolic enzymes) and liver (hepatic metabolic enzymes), (iv) effect of botanical drug components and/or their metabolites on intestinal or hepatic metabolic enzymes, and (v) effect of botanical drug components and/or their metabolites on transporters (Fig. 1) (Liu and Ling, 2006).

As the metabolites may be often present in complex matrix and at extremely low concentrations, highly specific and sensitive analytical methods are required. Liquid chromatography with mass spectrometric detection (LC-MS) is an ideal and widely used method in the analysis of metabolites owing to its superior specificity, sensitivity and efficiency (Kostiainen et al., 2003; Kamel and Prakash, 2006). Most of metabolite analyses are performed by using triple-quadrupole mass spectrometers because their tandem mass spectrometric (MS/MS) scan types are highly helpful in

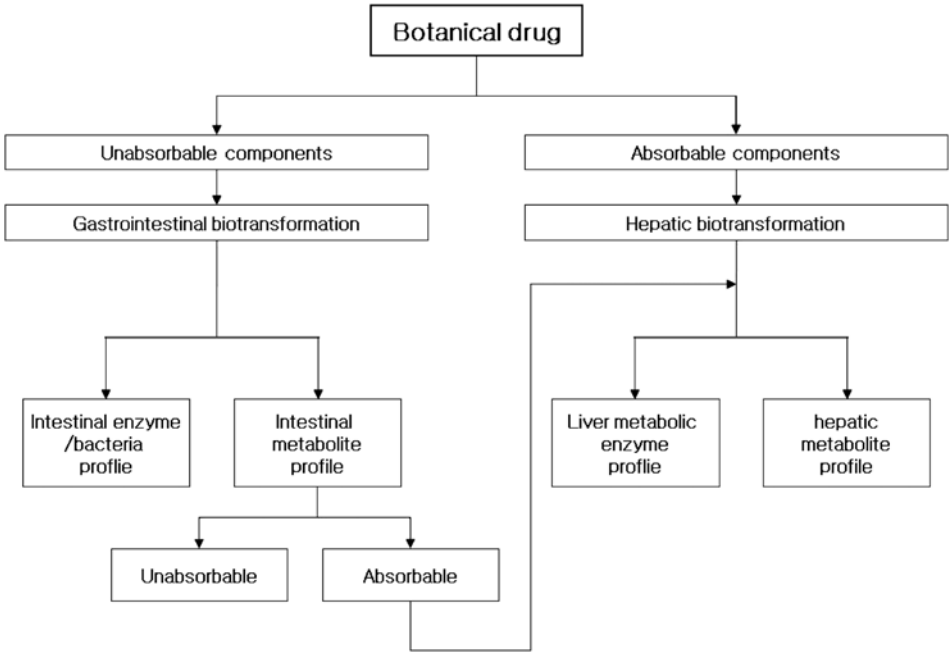

Fig. 1. *In vitro* characterization of botanical drug metabolism (Modified from Liu and Ling, 2006)

the identification of metabolites. Moreover, multiple reaction monitoring (MRM) provides high specificity and sensitivity required in quantitative analysis (Clarke et al., 2001).

In this issue, Song et al. (2010) shows *in vitro* metabolism study of jaceosidin, which is a pharmaceutically active ingredient found in *Artemisia* species as well as *Eupatorium* species and exerts antioxidant, anti-inflammatory, antiallergic, anticancer, and antimutagenic activities, by using LC-MS/MS. Authors identified that jaceosidin is metabolized to jaceosidin glucuronide, 6-*O*-desmethyljaceosidin, hydroxyjaceosidin, 6-*O*-desmethyljaceosidin glucuronide, and hydroxyjaceosidin glucuronide in human liver microsomal fractions. Moreover, they characterized human liver cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes responsible for the metabolism of jaceosidin. The results of this article suggest that the pharmacokinetic properties of jaceosidin may be affected by CYP and UGT enzymes responsible for jaceosidin metabolism and their inducers or inhibitors.

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