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Editorial

Metabolism Study Builds the Bridge from Research to Development

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Icaritin is an active prenylflavonoid derived from genus *Epimedium* L., a Chinese materia medica. Icaritin has a wide range of pharmacological and biological activities, including cardiovascular function improvement, hormone regulation, and antitumor activity.

From 1999 to 2015, the studies on the metabolism of icaritin have published about 60 research papers including icariin, its metabolites determination and pharmacokinetics. The previous study demonstrated that icariin, a glucoside of icaritin, was biotransformed its metabolites in rats by phase I and phase II metabolic pathway, including hydrolysis, demethylation, dehydrogenation, and glucuronidation. Icaritin was one of the metabolite of icariin in the body, by the hydrolysis of glucosidic bond, therefore, it might have the similar biotransformation process with that of icariin. Several published studies for the metabolite profiles of the components from the plants of genus *Epimedii* L., which mainly focused on the metabolism of icariin and other icaritin glycosides on zebrafishes. The glycoside hydrolysis and further glucuronidation are the major metabolism processes of these prenylflavonoids. While, up to now, icaritin metabolites are not directly anayzed except using zebrafishes.

In the article titled “Identification of Icaritin Metabolites in Rats by LC-MS/MS” (CHM 2015, 7(4): 296-302), researchers established a novel LC-MS/MS system with sensitivity and selectivity to analyze the icaritin metabolites in biological samples. The results on metabolite analysis are helpful to understand the metabolic pathway of icaritin and further investigate the pharmacological mechanism.

Researchers found that the conjugated metabolites by glucuronidation, glycosylation, and sulfation were the major metabolites of icaritin. In addition, a small amount of icaritin oxidates, demethylicaritin, and its isomers were also detected, suggesting that phase II metabolism might be the main metabolic pathway of icaritin. The enzymes involved in the synthesis of these phase II metabolites might be glucuronosyltransferase and sulfotransferase, which have been found in the small intestine. Different metabolites may display different pharmacokinetic profiles and excretion routes due to their different chemical structures, which would be involved with different metabolite enzymes and transportation rates. In the detection of metabolites, two metabolites were found not only in plasma but also in urine, indicating that the two metabolites might not be mainly excreted from the kidney. In contrast, six metabolites were found not only in urine but also in plasma, indicating that these metabolites might be rapidly excreted into urine after their formation.

Recurrent years, icaritin development is a hot-point in anticancer agents. The compound induces the apoptosis through caspase-dependent pathways in hepatocellular carcinoma (HCC). Before clinical trial, Tianjin Institute of Pharmaceutical Research (TIPR) carried out the preclinical studies on pharmaceutical technology, drug formulation, safety pharmacology, pharmacokinetics, toxicokinetics, and safety evaluation in experimental animals. Especially for solving formulation difficulties, researchers gained inspiration and enlightenment from the classic Chinese medicine processing methods for formulation process with high bioavailability, preparation of clinical formulations and the formulation industrial research, and the development has laid a grass-roots foundation. TIPR preclinical studies of new drug candidate laid a solid foundation to enter the clinical trials of the new drug candidate.

In 2012, the candidate has entered the clinical trials of new drugs in China. Shenogen Gruop’s R&D got supported from National Twelfth Five-year Plan on Special Innovation Project of New Drug Development. Icaritin treatment research in advanced HCC phase II clinical trial is completing. As known, HCC is a highly malignant cancer with poor prognosis and limits the treatment options. If further study on antitumor activities in advanced HCC patients will be established, the novel drug will have a positive impact for the treatment of advanced HCC patients.

Metabolism builds the bridge from research to development. We look forward to the published drug metabolism data being meaningful on understanding the advantages and characteristics of the drug, also look forward to the information being useful in understanding and explanation for the issues in clinical application after post-market.