Cytotoxic and P-Glycoprotein Modulating Effects of Thai Plant Extracts in Cancer Cells

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[Objective] We have recently examined the effects of Thai plant extracts on paclitaxel-resistant HepG2 (PR-HepG2) cells, and reported that KP018 has a potent cytotoxic effect, while AT80 and MM80 may be useful as modulators of P-glycoprotein (P-gp)-mediated multidrug resistance. In the present study, we examined whether these extracts would induce apoptosis or necrosis in PR-HepG2 cells using flow cytometry. In addition, the effects of these extracts on another cancer cell line colon-26 were examined.

[Methods] Ethanol extracts of Thai plants examined were KP018 from Ellipeiopsis cherrevensis, AT80 from Ancistrocladus tectorius, and MM80 from Micromelum minutum. Cancer cell lines employed were PR-HepG2 cells and colon-26 cells. Cytotoxic effects of the extracts were evaluated by XTT assay and flow cytometry.

[Results and Discussion] In contrast to cancer drugs like camptothecin, KP018 predominantly induced necrosis in PR-HepG2. When combined with paclitaxel, AT80 increased both necrotic and apoptotic cells while MM80 increased necrotic cells. Similar to the effects in PR-HepG2 cells, KP018 showed most potent cytotoxic effect in colon-26 cells among these extracts. The effects of these extracts on P-gp function in colon-26 cells will also be discussed.

[Conclusions] These Thai plant extracts may be useful sources to search for new anticancer drugs.

Metabonomic Approach for Identifying Endogenous and Food-Derived Substrates of MRP2 in Rats

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[Objective] Drug transporters play significant roles in the disposition of endogenous substrates as well as xenobiotics. Metabonomics deals with the comprehensive analysis of low molecular weight components in a biological sample, and will provide new insight into the role of drug transporters by identifying endogenous and food-derived substances, the disposition of which is tightly regulated by transporter function. In the present study, we performed a metabonomic analysis using Eisai-hyperbilirubinemic rats (EHBHR), which are hereditarily deficient in Mrp2/Abcc2, resulting in the accumulation of glucuronide conjugates, such as bilirubin glucuronide, and sulfate conjugates of bile acids.

[Methods] Plasma, bile and urine specimens were collected from bile duct–cannulated EHBHR (male, 7 weeks old) and Sprague Dawley rats (SDR), then subjected to a comprehensive LC/MS analysis.

[Results and Discussion] Principle component analysis (PCA) score plots based on the peak intensities of plasma components (~2,000 peaks) detected using the LC/MS analysis demonstrated an acceptable classification into EHBHR and SDR. A number of compounds accumulated in the plasma of the EHBHR rats, compared with the plasma of SDR rats, including sulfoglucuronides of phytoestrogen-related compounds (> 40 fold) and bilirubin diglucuronide, the biliary excretions of which were lower in bile from the EHBHR rats.

[Conclusions] These results suggest that phytoestrogen-related compounds are eliminated into the bile by Mrp2 as sulfoglucuronides.