Abstract

This work is based on two attached first authors' publications dealing with the effect of natural substances of plant origin on transcriptional activity of nuclear and steroid receptors and their action on cytochrome P450 expression, CYP1A subfamily. The studied substances are anthocyanidins and stilbenes, belonging to a broad group of phenolic compounds.

The aim of the first study was to evaluate the effect of the most common anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, and peonidin) on the transcriptional activity of nuclear and steroid receptors. The activities of nuclear receptors: vitamin D receptor (VDR), retinoid X receptor (RXR), retinoic acid receptor (RAR), pregnane X receptor (PXR), thyroid receptor (TR), and steroid receptors: progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), and glucocorticoid receptor (GR) were assessed using either stable or transiently transfected luciferase gene reporter cell lines. The cytotoxicity assays and gene reporter assay were performed after the 24h treatment of cells with increasing range of concentrations (10 nM to 50 µM) of selected anthocyanidins. The results of experiments indicate that none of the studied anthocyanidins in all tested concentrations caused remarkable changes of transcriptional activity of examined steroid receptors, but their increasing concentrations slightly inhibited transcriptional activity of nuclear receptors induced by model agonists.

The aim of the second study was to describe the effects of thirteen different hydroxy- and methoxystilbenes, including their *cis/trans* isomers on the transcriptional activity of aryl hydroxycarbon receptor (AhR) and the expression of CYP1A genes in hepatic cancer cells HepG2 and primary human hepatocytes. Techniques of gene reporter assay, qRT-PCR, Simple Western blotting by Sally Sue[TM] and electrophoretic mobility shift assay (EMSA) were employed. All compounds activated AhR, but their efficacies, potencies and dose-response profiles differed substantially. The strongest activator of AhR and inducers of CYP1A1 in HepG2 cells were DMU-212 ((E)-3,4,5,4′-tetramethoxystilbene), *trans*-piceatannol, *cis*-piceatannol, *trans*-trismethoxyresveratrol and *trans*-pinostilbene. While DMU-212 and *trans*-trismethoxyresveratrol also induced CYP1A1 and CYP1A2 in primary human hepatocytes, the effects of *trans*-piceatannol, *cis*-piceatannol and *trans*-pinostilbene weaned off. On the other hand, trans-4-methoxystilbene was strong CYP1A inducer in primary hepatocytes but not in HepG2 cells. Differences between effects of stilbenes in HepG2 cells and primary hepatocytes are probably due to the extensive phase I and phase II xenobiotic metabolism in primary hepatocytes. The data obtained may be of toxicological relevance.