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Metabolomics study of early metabolic changes in hepatic HepaRG cells in response to rosemary diterpenes exposure

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Abstract

Rosemary diterpenes have demonstrated diverse biological activities, such as anti-cancer, antiinflammatory, as well as other beneficial effects against neurological and metabolic disorders. In particular, carnosic acid (CA), carnosol (CS) and rosmanol (RS) diterpenes have shown interesting results on anti-cancer activity. However, little is known about the toxic effects of rosemary diterpenes at the concentrations needed to exert their antiproliferative effect on cancer cells. In our study, CA, CS and RS exhibited a concentration-dependent effect on cell viability of two human colon cancer cell lines (HT-29 and HCT116) after 24 h exposure. HT-29 cell line was more resistant to the inhibitory effect of the three diterpenes than HCT116 cell line. Among the three diterpenes, RS exerted the strongest effect in both cell lines. To investigate the hepatotoxicity of CA, CS and RS, undifferentiated and differentiated HepaRG cells were exposed to increasing concentrations of the diterpenes (from 10 to 100 μM). Differentiated cells were found to be more resistant to the toxic activity of the three diterpenes than undifferentiated HepaRG, probably related to a higher detoxifying function of differentiated HepaRG cells compared with the undifferentiated cells. The metabolic profiles of differentiated HepaRG cells in response to CA, CS and RS were examined to determine