Title: Effects of oridonin on hepatic cytochrome p450 expression and activities in pxr-humanized mice

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Abstract:
BackgroundOridonin, the major terpene found in Rabdosia rubescens, is widely used as dietary supplement or therapeutic drug, while the effects of oridonin on CYP450 were still unclear [1]. The pregnane X receptor (PXR) is an important regulatory factor for major drug metabolism enzyme cytochrome P450 (CYPs), and it has been reported to species-specific differences .The PXR-humanized mice are genetically similar to humans, and therefore are widely used as medical experimental animals to predict drug effects on downstream metabolic enzymes of PXR[2].MethodsEight-week-old male PXR-humanized mice were treated with oridonin by orally (0, 25, 50, 100, 200 mg/kg, i.g.) for 15 days. The effects of oridonin on major downstream Cyps of PXR were examined at both the mRNA and enzyme activity levels by RT-PCR and HPLC-MS/MS[3,4].ResultsIn general, there was no significant toxic reaction in liver of PXR-humanized mice. While the mRNA expression of Cyps and POR were increased with oridonin treatment in a dose-dependent manner. Cyp2c and Cyp3a family catalytic activity were increased significantly in two higher doses groups.ConclusionThese results indicate that oridonin induced the expression and activation of Cyp2c and Cyp3a family, which might contribute to potential drug-drug interactions and appear to be a risk when co-administered with other clinical drugs.References[1] Chen XW, B Sneed K, Pan SY, et al. Herb-drug interactions and mechanistic and clinical considerations. Current drug metabolism 13, 13(5), 640-651(2012). [2] Xie W, Barwick JL, Downes M, et al. Humanized xenobiotic response in mice expressing nuclear receptor SXR. Nature, 406(6794), 435(2000).[3] De Bock L, Boussery K, Colin P, et al. Development and validation of a fast and sensitive UPLC-MS/MS method for the quantification of six probe metabolites for the in vitro determination of cytochrome P450 activity. Talanta, 89, 209-16(2012).[4] Guo Y, Pope C, Cheng X, et al. Dose-response of berberine on hepatic cytochromes P450 mRNA expression and activities in mice. J Ethnopharmacol, 138(1), 111-8(2011).