Glycyrrhizin has a high likelihood to be a victim of drug-drug interactions mediated by hepatic organic anion-transporting polypeptide 1B1/1B3

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- Supporting Information Appendix S2 -

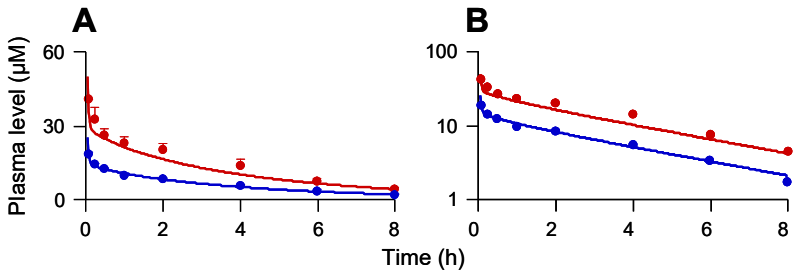

Figure S1

Observed (dots) and retrospectively predicted plasma concentrations (lines) of rifampin over time after an i.v. bolus dose of rifampin at 10 (in blue) and 20 (in red) $mg \cdot kg^{-1}$ in rats. The observed concentrations of rifampin (solid circles), representing means and standard deviations, are obtained from the rat data reported by Jiang *et al.* (2015). The PBPK model for i.v. rifampin was developed in this investigation (Table S2 in Supporting Information Appendix S1). Panels A and B are arithmetic and semilogarithmic plots, respectively.

Reference

Jiang R-R, Dong J-J, Li X-X, Du F-F, Jia W-W, Xu F *et al.* (2015). Molecular mechanisms governing different pharmacokinetics of ginsenosides and potential for ginsenoside-perpetrated herb-drug interactions on OATP1B3. Br J Pharmacol 172: 1059–1073.

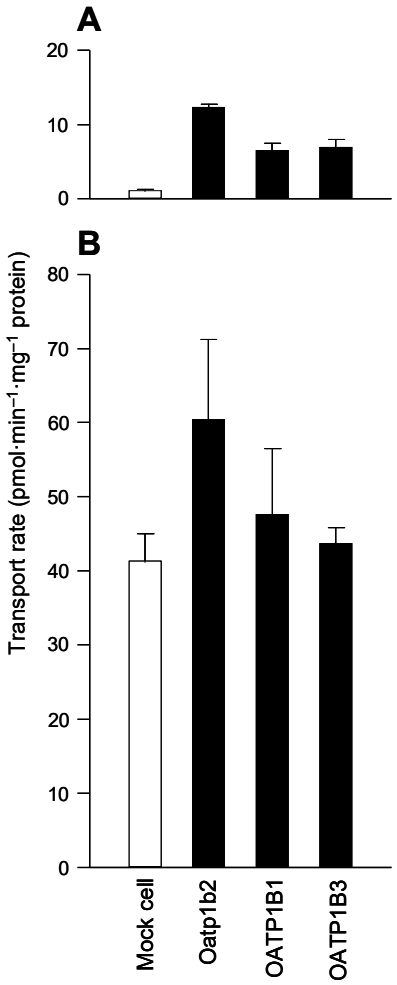

Figure S2
Transport of glycyrrhizin (A) and rifampin (B) in HEK-293 mock cells and rat Oatp1b2-, human OATP1B1- and human OATP1B3-expressing HEK-293 cells. The transport values represent the means ± SDs (*n* = 3).

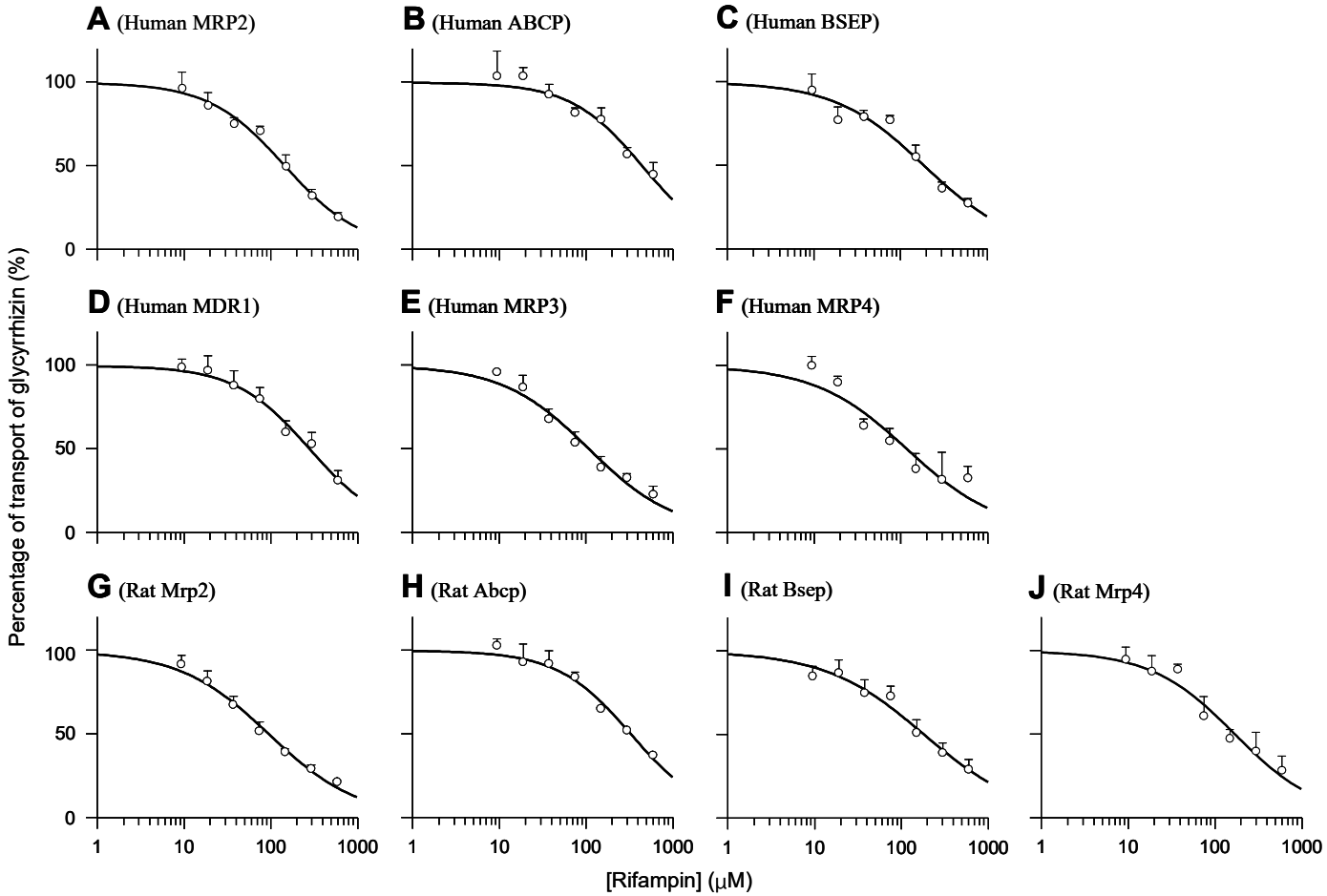

Figure S3

Representative IC_{50} plots of rifampin inhibition of human MRP2- (A), human ABCP- (B), human BSEP- (C), human MDR1- (D), human MRP3- (E), human MRP4- (F), rat Mrp2- (G), rat Abcp- (H), rat Bsep- (I) and rat Mrp4-mediated vesicular transport of glycyrrhizin (J). The IC_{50} values are shown in Table 2, and they represent the means ± SDs (n = 3). The concentration of the substrate glycyrrhizin was 50 μM for all the test transporters. The concentrations of the inhibitor rifampin were 0–600 μM for all the test transporters.

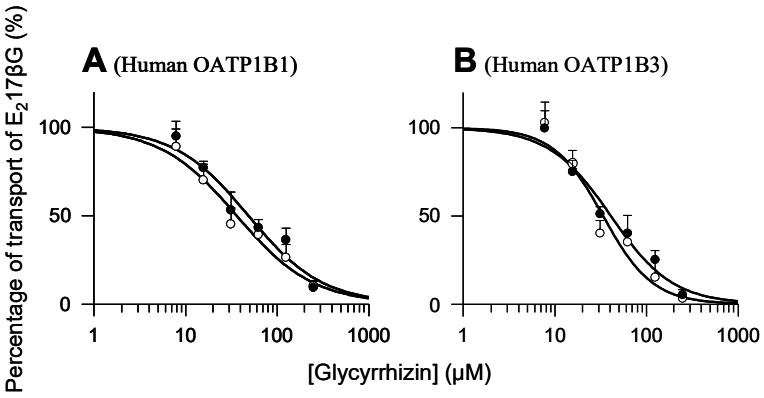

Figure S4

IC_{50} plots of glycyrrhizin inhibition of human OATP1B1- (A) and human OATP1B3-mediated cellular uptake of $E_2$17βG (B) after 1-h preincubation with glycyrrhizin in the absence of the substrate $E_2$17βG (solid dots) and after such preincubation without glycyrrhizin (open dots). The IC_{50} values represent the means ± SDs (n = 3). The concentrations of glycyrrhizin were 0–250 μM and the concentration of $E_2$17βG was 10 μM.

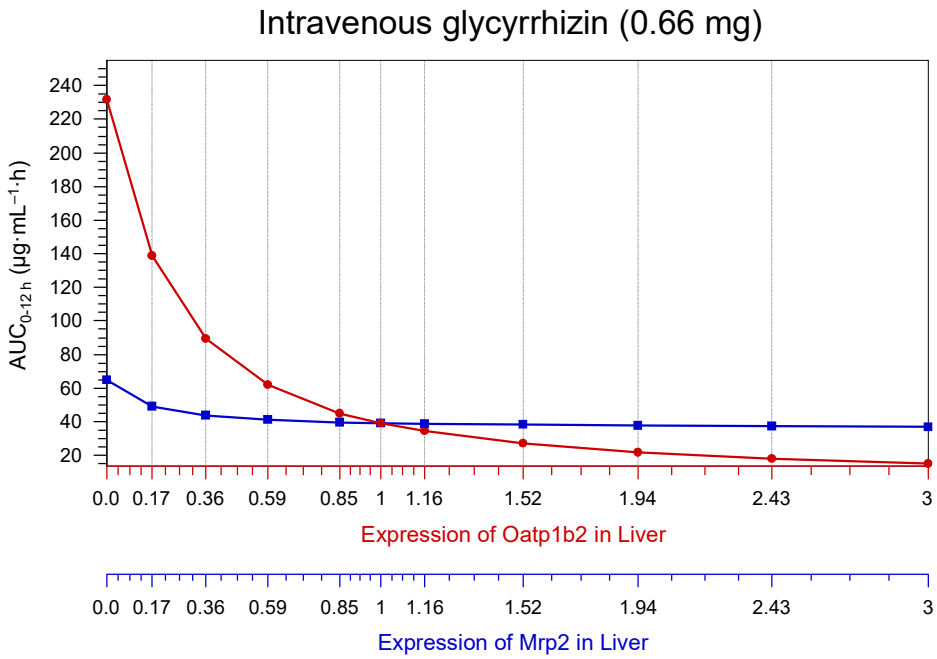

Figure S5

Parameter sensitivity analysis (PSA) plot for relationship of expression of Oatp1b2 and Mrp2 in the rat liver to plasma $AUC_{0\text{-}12\ h}$ of glycyrrhizin.