Cytosolic β-glucosidase inhibition and renal blood flow suppression are leading causes for the enhanced systemic exposure of salidroside in hypoxic rats

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Objectives
To investigate the pharmacokinetics of salidroside in hypoxic rats; to explore the underlying mechanisms for the distinct metabolic fate of salidroside under hypoxia and to construct physiologically based pharmacokinetic (PBPK) models capable of predicting salidroside plasma concentrations in both normoxic and hypoxic rats.

Methods
Pharmacokinetic studies were conducted in both hypoxic and normoxic rats to obtain key parameters for PBPK model construction, including the in-vivo clearance (CL), the volume of distribution (Vd) and the concentration-time profile of salidroside. The apparent permeability coefficient (Papp) of salidroside was measured via both hypoxic and normoxic Caco-2 monolayer models. Enzymes involved in salidroside metabolism were identified by specific chemical inhibitors. The Vmax, Km, and Clint values of crucial enzymes involved in salidroside metabolism were determined in-vitro by rat liver homogenate incubation and then scaled-up with the aid of Gastro-plus for PBPK model construction. The renal clearance (CLR) of salidroside, the effective renal plasma flow (ERPF) and the glomerular filtration rate (GFR) in both hypoxic and normoxic rats were also determined for renal function assessment. The PBPK models were constructed with consideration of multi-factors, including absorption, whole-body distribution, renal clearance, metabolic conversion, and permeability-limited hepatic disposition of salidroside.

Results
The systemic exposure of salidroside in hypoxic rats was remarkably higher than that in normoxic rats. Hepatic metabolism of salidroside in hypoxic rats was attenuated due to the reduced activity of cytosolic β-glucosidase (CBG). Moreover, CLR of salidroside was reduced in hypoxic rats due to the suppressed ERPF. The scaled-up PBPK model provided an excellent prediction for the systemic exposure, CL and Vd of salidroside in both normoxic and hypoxic rats.

Conclusion and Implications
CBG inhibition and ERPF suppression were leading causes for the enhanced systemic exposure of salidroside in hypoxic rats. The PBPK model developed in this study was capable of accurately predicting the plasma salidroside concentrations in both normoxic and hypoxic rats, and provided insight into the physiological factors that determine salidroside absorption and disposition. Our findings disclosed crucial physiological changes in hypoxic animals and suggested the potential needs for dose-adjustment of salidroside or its structural analogs under hypoxic conditions.