Pharmacokinetics and Pharmacodynamics Interaction between Oseltamivir and Radix Scutellariae in Sprague Dawley Rats

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Purpose
Oseltamivir (O) is a potent and selective inhibitor of the neuraminidases glycoprotein and approved for the treatment and prophylaxis of influenza around the world. Based on our previous screening of eight Chinese herbs and their ten marker components via our established in-vitro absorption, metabolism and anti-virus screening platform, Radix Scutellariae (RS) has been identified to have the most potential for herb-drug interaction with O. The current study aims to provide in-vivo verification for the pharmacokinetics and pharmacodynamics herb-drug interaction between RS and O in Sprague Dawley (SD) rats.

Methods
Sixty SD rats were randomly divided into six groups (G1 to G6, n=10/group), which received a dose twice daily for 5 days according to the following combination of O (30 mg/kg) and 300 mg/kg RS extract (1xRS) or 600 mg/kg RS extract (2xRS) with specific groupings of G1: O + Water; G2: O + 1xRS; G3: O + 2xRS; G4: Water + 1xRS; G5: Water + 2xRS; G6: 2xWater only. After the first dosing on Day 5, blood samples (0.2 mL each) were withdrawn via the jugular vein catheter at 0, 15, 30, 60, 90, 120, 180, 240, 360 and 480 min post dose. At 30 min following the last dosing on Day 5, the rats were anesthetized and about 10 mL of blood were collected from rats’ inferior vena for determination of antiviral activity again H1N1 and H3N2 via a plaque reduction assay. All rat plasma samples were analyzed by an LC/MS/MS method to determine the concentrations of O and its active metabolite oseltamivir acid (OA).

Results
Co-administration of O with RS (G1, G2, G3) could significantly increase the AUC and Cmax of O and decrease those of OA, however without a dose-dependency on RS. A subsequent lower cumulative amount ratio of OA/O in rat urine for groups G2 and G3 (Figure 1) was observed. When compared to the control group (G6), the RS herb only groups (G4 and G5) did not show a significant reduction in virus plaque of either H1N1 or H3N2, suggesting no antiviral effect of RS. In the meantime, a significant reduction in the number of virus plaque (both H1N1 and H3N2) was observed for all O treated groups (G1, G2, and G3), which was not significantly altered after co-administration of RS extracts with O (G2 and G3). Such lack of significant difference in antiviral effect between G1 and G2&G3 can be further reflected by the similar OA concentrations (p>0.05 for two-tailed t-test) of 719.4416.8, 502.883.7 and 460.4143.5 ng/mL, for G1, G2, and G3, respectively.

Conclusion
Our in-vivo rat model verified that co-administration of O with RS could increase the systemic exposure of O and decrease the systemic exposure of OA, but not influence its overall anti-virus effects. (Health and Medical Research Fund, Reference number: 11120451)

![Figure 1.](image-url) Plasma concentration versus time profiles of oseltamivir (O) and oseltamivir acid (OA) after oral administration of O (30 mg/kg) + Water (A), O + 1*Herb (Radix Scutellariae, 300 mg/kg) (B) and O + 2*Herb (Radix Scutellariae, 600 mg/kg) (C). Comparison of cumulative amount of OA/O in urine (D) (n=10)