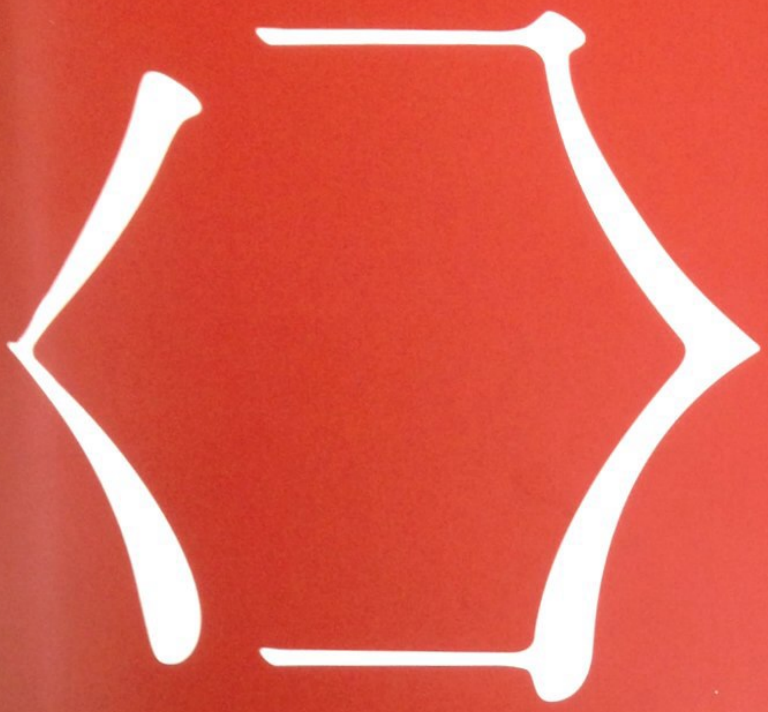

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Coptidis Rhizoma Decreased the Oral Bioavailability of Cyclosporine Through Potential Activation of P-glycoprotein and CYP3A4

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Abstract. Coptidis Rhizoma (CR), rhizome of *Coptis chinensis*, is a Chinese herb (Huanglian) used for the treatments of intestinal infections, cancers and inflammation-related diseases. CR contains isoquinoline alkaloids such as berberine, coptisine and palmatine. Cyclosporine (CSP), an important immunosuppressant with narrow therapeutic window, is a substrate of P-gp and CYP 3A4. This study investigated the effect of coadministration of CR on the pharmacokinetics of CSP, a probe substrate of P-gp and CYP 3A4. Rats were orally administered CSP with and without CR and blood samples were collected at specific time. The blood CSP concentration was determined by a specific monoclonal fluorescence polarization immunoassay. The underlying mechanisms were investigated by using cell model and recombinant CYP450 isozyme. The results showed that coadministration of a single dose and the 7th dose of 1.0 g/kg of CR significantly decreased the C_{max} of CSP by 56.9 % and 70.4 %, and reduced the $AUC_{0\text{-}540}$ by 56.4 % and 68.7 %, respectively. Mechanism studies indicated that CR decoction, berberine, coptisine, palmatine all activated P-gp, and the serum metabolites of CR activated CYP3A4. In conclusion, administration of CR resulted in markedly decreased bioavailability of CSP through activation of both P-gp and CYP 3A4.

Introduction. Coptidis Rhizoma (CR, rhizome of *Coptis chinensis* FRANCH), is often prescribed for the treatments of intestinal infections, diabetes mellitus, cancers and inflammation - related diseases in Asian countries. Cyclosporine (CSP), an important immunosuppressant with narrow therapeutic window, is a substrate of P-gp and CYP 3A4. It has been well known that P-glycoprotein (P-gp) and cytochrome P450 enzymes (CYP450s) play crucial roles in drug oral bioavailability and drug - drug interactions (1). Recent studies have reported that berberine, the major component in CR, exhibited biphasic effects on P-gp activity (2). In addition, an *in vitro* study reported that CR and its alkaloid constituents inhibited CYP3A4, CYP2D6 and CYP1A2 (3). Therefore, we hypothesized that when CR was concomitantly administered with CSP, the blood CSP levels might be affected. This study set out to investigate the influence of coadministration of CR on the pharmacokinetics of CSP

Materials and Methods. Drug administration was conducted in a parallel design. In the first group, six control rats received 2.0 mL/kg of water at 0.5 h before CSP (2.5 mg/1.0 mL/kg). In the second group, CR decoction (1.0 g/2.0 mL/kg) was orally given to five rats at 0.5 h before CSP. In the third group, five rats were given CR decoction twice daily and the 7th dose (1.0 g/2.0 mL/kg) was given at 0.5 h before CSP. The blood CSP concentration was determined by a specific monoclonal fluorescence polarization immunoassay. The underlying mechanisms were investigated by using LS180 cell model and recombinant CYP450 isozymes.

Results and Dicsussion. A single dose and the 7th dose of CR both significantly decreased the peak blood concentration and systemic exposure of CSP (Fig. 1). The interaction magnitudes of two treatments were comparable. Based on *in vitro* studies, the decreased absorption of CSP caused by CR was through activation of P-gp and CYP3A4, which additively enhanced the first-pass effect of CSP.

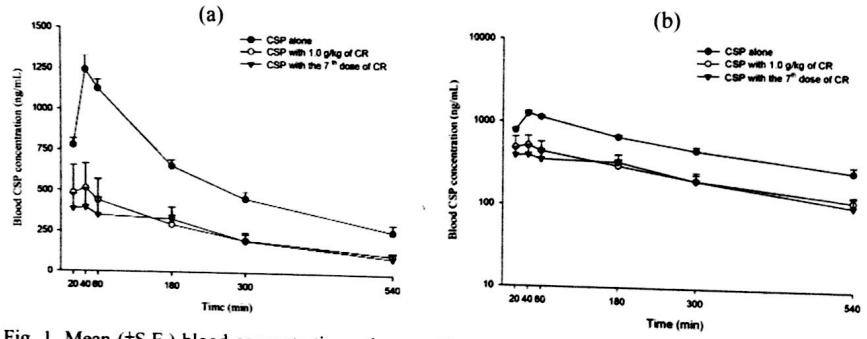

Fig. 1. Mean (±S.E.) blood concentration - time profiles of CSP after oral administration of CSP alone (2.5 mg/kg) (●) and coadministration with single dose (○) and the 7th dose (▼) of 1.0 g/kg of CR in rats (a) and the semi-log plot (b).

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