Green tea catechins affect the pharmacokinetics of simvastatin via the inhibition of intestinal cytochrome P450 3A activity in rats

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Green tea catechins have been reported to have antioxidant, anti-inflammatory, and anticancer properties. The wide variety of medical uses of green tea suggests that the possibility for coadministration with prescribed drugs, and accordingly, the potential for drug interactions, is high. Here, we investigated whether the green tea extract (GTE), containing 86.5% of catechins, would inhibit cytochrome P450 (CYP) 3A activity *in vitro*. The effect of GTE on the pharmacokinetics of simvastatin (SIM) and simvastatin acid (SVA, an active metabolite) in rats was also examined.

In rat liver microsomes, the mean inhibitory concentrations (IC_{50}) for GTE versus CYP3A (midazolam 1'-hydroxylation) was 7.8 μg/mL, suggesting the inhibitory effect of GTE on CYP3A activity. In animal experiments, SIM (20 mg/kg) was administered orally to female Sprague-Dawley rats at 30 min after single or repeated (7 days) ingestions of GTE (400 mg/kg) or saline (control). Plasma concentrations of SIM and SVA were measured up to 6 hours after SIM administration. In the single ingestion of GTE, the mean area under the time-concentration curve (AUC) and maximal peak plasma concentration (C_{max}) of SIM were significantly increased by 1.6- and 1.7-fold, respectively, as compared to control group. On the other hand, there was no significant difference in the elimination half-life of SIM between the single GTE and control group. Repeated ingestions of GTE also resulted in marked increases in AUC and C_{max} of SIM compared with control group. In addition, AUC and C_{max}, but not elimination half-life, of SVA tended to be higher in the GTE group after both single and repeated ingestions of GTE as compared to control. These results suggested that GTE could alter the pharmacokinetics of SIM and SVA in rats, possibly by inhibiting the intestinal CYP3A activity and subsequently reducing the first-pass effect of SIM.

In conclusion, the present study demonstrated that green tea catechins inhibited CYP3A activity and altered the plasma concentration profile of SIM and SVA in rats. Therefore, the clinical implication of the effects of green tea catechins on the bioavailability of SIM in human should be further evaluated.