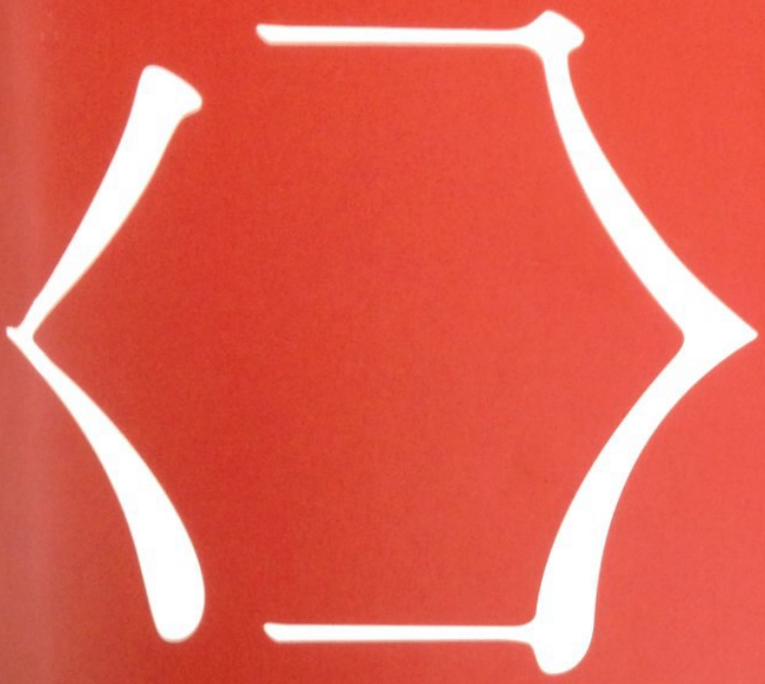

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Potential Modulation on BCRP and CYP 3A4/2D6 by Cranberry: *in vivo* and *in vitro* Studies

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Abstract Gefitinib is an epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI) used for treating patients with non-small cell lung cancer. The oral bioavailability of gefitinib was associated with P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and cytochrome P450 3A4/2D6. Cranberry contains rich polyphenols and is often used for the prevention of urinary tract infections. This study investigated the effect of cranberry juice on gefitinib pharmacokinetics and the underlying mechanisms. Rats were administered gefitinib with and without 0.5 and 5.0 g/kg of cranberry. The serum gefitinib concentrations were determined by using LC-MS/MS. The results revealed that 5.0 g/kg of cranberry significantly increased the AUC_{0-t} and C_{max} of gefitinib by 55 and 24%, respectively, whereas 0.5 g/kg of cranberry did not alter the bioavailability of gefitinib. A further inquiry into the underlying mechanism indicated that the serum metabolites of cranberry inhibited the activities of BCRP, CYP 3A4 and CYP 2D6. In conclusion, concurrent ingestion of cranberry juice significantly increased the systemic exposure of gefitinib through inhibition on BCRP, CYP 3A4 and CYP 2D6.

Introduction. Gefitinib (Iressa®) is an epidermal growth factor receptor - tyrosine kinase inhibitor (EGFR-TKI) used for treating patients with non-small cell lung cancer. Gefitinib has been demonstrated as substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which have been recognized to play important roles in the bioavailability of gefitinib [1]. The metabolism of gefitinib occurs for the most part in the liver, primarily metabolized by CYP 3A4 and CYP 2D6, with CYP 3A5 playing a minor role [2]. Cranberry contains rich polyphenols and has popularly been used in the prevention of urinary tract infections [3]. Because numerous polyphenols have been reported to be modulators of P-gp, BCRP, CYP 3A4 and CYP 2D6, this study investigated the effects of cranberry juice on gefitinib pharmacokinetics in rats, and the relevant mechanisms were explored by using *in vitro* models.

Materials and Methods. Rats were administered gefitinib with and without 0.5 and 5.0 g/kg of cranberry. The serum gefitinib concentrations were determined by utilizing LC-MS/MS. LS 180 was used as a model for P-gp-mediated transport study. MDCKII-BCRP was used to evaluate the effect of cranberry on BCRP activity. Vivid® CYP 450 screening kits were used to evaluate the effects of cranberry on the activities of CYP 3A4 and CYP 2D6. An *ex-vivo* approach using the serum metabolites of cranberry to measure the [illegible] of CYPs and renal BCRP was conducted.

Results and Discussion. Concurrent intake of 5.0 g/kg of cranberry significantly increased the systemic exposure and the peak blood concentration of gefitinib by 55 and 24%, respectively, whereas 0.5 g/kg of cranberry exerted no alteration on the bioavailability of gefitinib (**Fig. 1** and **Table 1**). Mechanism studies revealed that P-gp was activated by cranberry, whereas BCRP, CYP 3A4 and CYP 2D6 were inhibited by cranberry metabolites. In conclusion, ingestion of cranberry juice significantly increased the peak serum concentration and systemic exposure of gefitinib through inhibition on BCRP, CYP 3A4 and CYP 2D6.

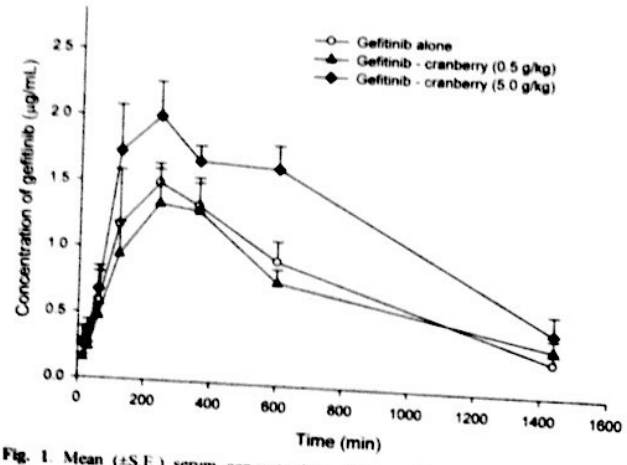

Fig. 1. Mean (±S.E.) serum concentration - time profiles of gefitinib [illegible] administration

Table 1. Mean (±S.E.) pharmacokinetic parameters of gefitinib after giving gefitinib alone and coadministration with 0.5 g/kg and 5.0 g/kg of cranberry.

Parameter \ Rats	Gefitinib alone	Gefitinib with cranberry (0.5 g/kg)	Gefitinib with cranberry (5.0 g/kg)
T_{max} (min)	264 ± 44.9	288 ± 29.4	216 ± 44.9
C_{max} (μg/mL)	1.8 ± 0.3[a]	1.5 ± 0.2[a]	2.3 ± 0.2[b] (+24%)
AUC_{0-t} (μg · min/mL)	1170.5 ± 129.3[a]	1072.8 ± 123.5[a]	1818.2 ± 144.8[b] (+55%)
MRT (min)	511.3 ± 40.1	564.4 ± 30.9	543.0 ± 29.8

T_{max}: time of occurrence for maximum drug concentration
C_{max}: maximum concentration of drug