Evaluation of the In Vitro/In Vivo Potential of Five Berries (Bilberry, Blueberry, Cranberry, Elderberry, and Raspberry Ketones) Commonly Used as Herbal Supplements to Inhibit Uridine Diphospho-Glucuronosyltransferase

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Purpose
In this study, we evaluated inhibitory potentials of popularly-consumed berries (bilberry, blueberry, cranberry, elderberry, and raspberry ketones) as herbal supplements on UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 in vitro. We also investigated the potential herb-drug interaction via UGT1A1 inhibition by blueberry in vivo.

Methods
Inhibitory effects on UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 by bilberry, blueberry, cranberry, elderberry, and raspberry ketones were evaluated in pooled human liver microsomes. β-Estradiol-3-glucuronide, trifluoperazine-N-glucuronide, serotonin-O-glucuronide, propofol-O-glucuronide, and zidovudine-5′-glucuronide formation activities were determined as probe activities in human liver microsomes for UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, respectively. Known inhibitors were included as positive controls to validate these experiments and compare 50% inhibitory concentration (IC50) values. Nilotinib (0-5 μM), hecogenin (0-500 μM), 1-naphthol (0-5000 μM), niflumic acid (0-50 μM), and efavirenz (0-200 μM) were used as positive control inhibitors of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, respectively.

Results
We demonstrated that these berries had only weak inhibitory effects on the five UGTs. Bilberry and elderberry had no apparent inhibitions. Blueberry weakly inhibited UGT1A1 with an IC50 value of 62.4 ± 4.40 μg/mL and a Ki value of 53.1 μg/mL. Blueberry also weakly inhibited UGT2B7 with an IC50 value of 147 ± 11.1 μg/mL. In addition, cranberry weakly inhibited UGT1A9 activity (IC50 = 458 ± 49.7 μg/mL) and raspberry ketones weakly inhibited UGT2B7 activity (IC50 = 248 ± 28.2 μg/mL). Among tested berries, blueberry showed the lowest IC50 value in the inhibition of UGT1A1 in vitro. However, the co-administration of blueberry had no effect on the pharmacokinetics of irinotecan and its active metabolite, SN-38, which was mainly eliminated via UGT1A1, in vivo.

Conclusion
Our data suggests that these five berries are unlikely to cause clinically significant herb-drug interactions mediated via inhibition of UGT enzymes involved in drug metabolism. These findings should enable an understanding of herb-drug interactions for the safe use of popularly-consumed berries.