Noncompetitive Inhibitory Effect of Myricetin on Folate Transport by Proton-Coupled Folate Transporter

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Purpose
Myricetin is a flavonoid that has recently been suggested to interfere with the intestinal folate transport system. The present study was conducted to examine that possibility, focusing on its inhibitory effect on proton-coupled folate transporter (PCFT/SLC46A1) as the molecular entity of the transport system.

Methods
The uptake of \[ ^3H \]folate was examined at an acidic condition of pH 5.5, where PCFT can operate efficiently, and at 37°C, using the Caco-2 cell line as an intestinal epithelial cell model and also the Madin-Darby canine kidney II (MDCKII) cell line stably expressing human PCFT. The cells were cultured and used on 24-well plates for the evaluation of folate uptake in the initial phase, 10 min for the former and 2 min for the latter. Myricetin and a few other flavonoids were added to the uptake medium at the concentration of 100 µM to examine their effect on PCFT-mediated folate uptake.

Results
The uptake of folate in Caco-2 cells was highly saturable with the Michaelis constant \( (K_m) \) of 0.407 µM and its carrier-mediated transport component was found to be noncompetitively inhibited by myricetin with the inhibition constant \( (K_i) \) of 61 µM. Folate transport by PCFT stably expressed in MDCKII cells was also highly saturable with the \( K_m \) of 1.246 µM and, consistent with the finding in Caco-2 cells, noncompetitively inhibited by myricetin with the \( K_i \) of 130 µM. Thus, overall, myricetin was suggested to inhibit intestinal folate transport by acting noncompetitively on PCFT, although the \( K_m \) and \( K_i \) were similarly shifted to be larger to some extent in Caco-2 cells. Finally, similar inhibitory effect was indicated for epigallocatechin-3-gallate (EGCG), but not for naringin.

Conclusion
Myricetin was suggested to inhibit intestinal folate uptake by acting noncompetitively on PCFT. It could be also caused by EGCG and possibly by some other flavonoids. Care may need to be taken, therefore, in the ingestion of myricetin and certain flavonoids to maintain the absorption of folates and antifolate drugs.