The study of the interaction between ampelopsin, myricetin, and their sulfate conjugates and multispecific organic anion-transporting polypeptides (OATP1B1, OATP2B1)

SpT-14-1

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Organic anion-transporting polypeptides (OATPs) are membrane transporters that facilitate the cellular uptake of various organic substances. Among them, OATP1B1 is a key uptake transporter in hepatic detoxification. Hence, OATP1B1 inhibition through food-drug and drug-drug interactions could lead to adverse effects. Additionally, the ubiquitously expressed OATP2B1 is essential for the intestinal absorption of many orally administered drugs. Flavonoids, known for their beneficial biological effects, such as ampelopsin and myricetin are commonly present in various foods and beverages. Yet, except for myricetin, no data have been reported about the potential inhibitory effect of these flavonoids on OATPs. Therefore, in the current study, we investigated the interactions between OATP1B1 and OATP2B1 and ampelopsin, myricetin, and their sulfate metabolites using the fluorescence-based indirect assay developed earlier in our laboratory. Our research revealed that most of the flavonoids tested are strong inhibitors of OATP1B1 and OATP2B1 transport activity with low micromolar or even nanomolar IC50 values. In addition, we investigated potential flavonoid uptake with the help of 2-aminoethoxydiphenyl borate (2-APB), a cell-permeable molecule that, upon forming a complex with flavonoids, leads to enhanced fluorescence and allows fluorescence-based detection of certain flavonoids. Based on this method, we identify myricetin-3'-sulfate as a transported substrate of OATP1B1 and OATP2B1 for the first time. Our findings show that not only the original flavonoids but also some of their conjugates can interact with OATPs. Consequently, high intake of ampelopsin, myricetin, and their sulfate metabolites may disrupt the pharmacokinetic profiles of OATP substrate medicines. Furthermore, OATP1B1 and OATP2B1 can promote transcellular movement of the otherwise poorly cell-permeable myricetin-3'-sulfate.