Phenytoin and Cyclosporin-A suppress the expression of MMP-1 and TIMP-1 and Cathepsin L, but not that of Cathepsin B in cultured gingival fibroblasts.

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Abstract

Quercetin is a flavonoid most widely and abundantly present as glycosides in herbs and plant foods. However, detailed information concerning the metabolic pharmacokinetics of quercetin glycosides in vivo still remained limited. The aim of this study was to investigate the metabolic pharmacokinetics of quercetin and quercetin - rich herbs in rats and humans.Quercetin was administered intravenously (10 mg・kg -1, 33.1 mol・kg -1) and orally (50 mg・kg -1, 165.4 mol・kg -1) to rats. Blood samples were withdrawn via cardiopuncture at specific time points. An HPLC method was used to determine the concentrations of quercetin prior to and after hydrolysis using -glucuronidase and sulfatase, respectively. The pharmacokinetic parameters were calculated using noncompartment model of WINNONLIN. The results showed that after intravenous administration of quercetin, 93.8 % of the dose was circulating as its sulfates and glucuronides. After oral administration of quercetin, quercetin sulfates and glucuronides were exclusively present in the bloodstream, whereas the parent form of quercetin was not detected. The oral absorption rate of quercetin was 53 % compared to intravenous administration after dose correction. After oral administration of St John’ s Wort (containing quercetin glycosides 20.5 mol・kg -1) and onion juice (containing quercetin glycosides 10.3 mol・kg -1), quercetin sulfates and glucuronides were exclusively present in the bloodstream. However, in ginkgo decoction (containing quercetin glycosides 10.0 mol・kg -1), neither quercetin nor its conjugated metabolites was detected in the bloodstream.Healthy male volunteers ingested traditional decoction and commercial extract powder of Sophora japonica L. which contained equivalent amount of rutin (613.8 mol), a rutinoside of quercetin, in a randomized crossover design. The concentrations of rutin, quercetin, quercetin sulfates and glucuronides in urine were determined by HPLC prior to and after enzymatic hydrolysis with sulfatase and -glucuronidase, respectively. Neither rutin nor quercetin was detected, the predominant forms were quercetin sulfates

and glucuronides. Comparison of the urinary excretion of quercetin conjugated metabolites indicated that quercetin sulfates was significantly higher by 316.6 % and glucuronides by 294.3 % after dosing of commercial extract powder.When rats were administered with multiple doses of quercetin and quercetin - rich herbs, quercetin sulfates and glucuronides were exclusively present in the bloodstream, whereas quercetin was not detected. The tissue homogenates hydrolyzed with sulfatase and -glucuronidase, respectively, showed that quercetin conjugated metabolites, predominately quercetin sulfates, existed in liver and kidney. Neither quercetin nor its conjugated metabolites were detected in brain.Recently, reports concerning herb-drug interaction are increasing. Cyclosporin is an important immunosuppressant with narrow therapeutic window. It is a substrate for cytochrome P-450 (CYP) 3A4 and P-glycoprotein (Pgp). Any agent affecting CYP 3A4 and/or Pgp would interact with cyclosporine and cause adversed effects. In this study, oral coadministration of St John's Wort, ginkgo and onion to rats significantly decreased the oral bioavailability of cyclosporin, whereas substantially no influence was shown for intravenous cyclosporin. This indicates that the interactions between cyclosporin and St John's Wort, ginkgo or onion occurred mainly at the absorption site.In conclusion, quercetin sulfates and glucuronides were exclusively present in the bloodstream and tissues whether quercetin or its glycosides were administered. In order to ensure the efficacy of cyclosporine, we suggest that concurrent intake of cyclosporine with St John's Wort, ginkgo and onion, are better avoided.