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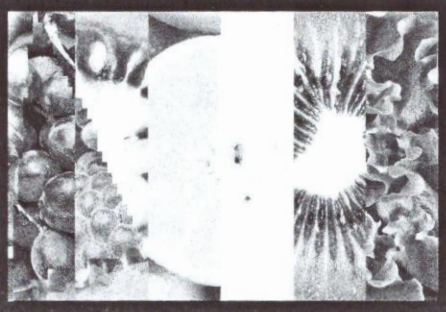

INRA SCIENCE & IMPACT

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Soy isoflavone daidzein increases the expression of NaPi 2a cotransporter in a rat model of the andropause

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Sodium phosphate cotransporter type 2a (NaPi 2a) is specifically expressed in the brush border membrane of renal proximal tubules and mediates the phosphate reabsorption from the primary urine. One of the main soy isoflavones, daidzein, has been widely studied for its therapeutic potential and already recognized as the bone protective substance. Aim of this study was to investigate the effects of daidzein application on NaPi 2a expression, phosphate and parathormone concentration in a rat model of the andropause.

Middle-aged Wistar rats were divided in three groups: sham operated (SO), orchidectomized (Orx) and daidzein treated orchidectomized group (Orx+D). Daidzein (30 mg/kg b.w.) was subcutaneously applicated, while the control groups received the vehicle alone. Expression of NaPi 2a was determined by RT-PCR and Western blot, while the serum and urine parameters were analyzed biochemically.

The abundance of NaPi 2a cotransporter expression was decreased in Orx animals in comparison with the SO group, while daidzein treatment enhanced the cotransporter expression when compared to the Orx rats. Serum phosphate concentration was decreased in Orx rats by 13% ($p<0.05$) in comparison with the SO group. Daidzein treatment elevated the serum phosphate by 10% ($p<0.05$) when compared to the Orx animals. Serum PTH concentration was increased after Orx in comparison with SO by 24% ($p<0.05$), while daidzein application decreased the same parameter by 18% ($p<0.05$) when compared to the Orx animals.

Our results demonstrated that daidzein treatment increases NaPi 2a cotransporter expression in the kidney of andropausal rats, which suggests some benefit of daidzei application when it comes to the regulation of mineral metabolism in advanced age.

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Generation and identification of quercetin phase-II metabolites to study drug transporter interactions

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Polyphenols are a large class of natural compounds which can interact with intestinal membrane drug transporters and thus possibly alter drug disposition. Polyphenols also undergo extensive intestinal phase-II metabolism, and these metabolites themselves can also be active towards drug transporters. This project aims to study the interactions of polyphenols and their metabolites with the major intestinal drug transporters P-gp, BCRP and MRPs. Quercetin was chosen as a model compound to develop assays and analytical methods to produce and identify phase-II metabolites, which will also be used for transporter interactions studies.

Quercetin and isorhamnetin (3'-O-methylquercetin) were incubated with HT29 cells for 24 h with samples taken at various time points. The chemical stability of quercetin in the medium alone was also investigated. The samples were analysed using UPLC-MS and Ion-Mobility Spectrometry (IMS).

Quercetin was completely metabolized after 4 hours, while showing a good chemical stability for the same period of time. Quercetin produced 7 detectable phase-II metabolites, glucuronides and methyl glucuronides, which were tentatively attributed based on retention times, MS data and previously published material. Isorhamnetin produced as expected only 2 metabolites, which confirmed the tentative attribution. IMS showed a significant difference in drift time between the different glucuronides, and thus could be used as an additional identification tool.

The developed strategy will be applied to other polyphenols selected through structural cluster analysis. These compounds and their metabolites will then be tested in transporter assays in order to build a predictive computational model for drug interactions.

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