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Shotgun metabolomics for mechanistic elucidation of the anti-obesity effects of xanthohumol from Hops (*Humulus lupulus*)

Xanthohumol is a prenylated flavonoid found in hops, beer and in dietary supplements. Zucker fa/fa rats, a model of obesity and metabolic syndrome were treated for six weeks with xanthohumol at four dose levels and measured metabolome profiles in addition to single endpoints of glucose and lipid homeostasis. Metabolomics analyses were conducted to identify biochemical pathways affected by xanthohumol treatment. The overall objective of the study was to gain a mechanistic understanding of the beneficial effects of xanthohumol in the treatment of metabolic syndrome. The highest dose group (16.9 mg/kg body weight, n=6) had significantly lower plasma glucose levels and smaller body weight gain compared to the control group (n=6) in male but not female rats. Food intake was not affected by treatment. It was detected >5000 metabolites by LC-QToF mass spectrometry, of which 133 metabolites were identified by mass, isotope distribution, MS/MS fragmentation pattern, and when standards were available, retention time. The shotgun metabolomics analyses showed a dose-dependent decrease of metabolic products of dysfunctional lipid metabolism (medium-chain acylcarnitines, dicarboxy fatty acids, hydroperoxy and hydroxy fatty acids). Taken together, the results indicate that xanthohumol improves β -oxidation of fatty acids by mild mitochondrial uncoupling, which we verified by time-course metabolomics and measurements of oxygen consumption rates in cultured mouse skeletal muscle (C₂Cl₂) cells treated with xanthohumol. Xanthohumol improves β -oxidation of fatty acids and increases energy expenditure by mild mitochondrial uncoupling, resulting in an overall beneficial effect on markers of metabolic syndrome.

Biography

Jan Frederik Stevens received his MSc in Pharmacy (1988), pharmacy license (1990), and PhD in Medicinal Chemistry (1995) from Groningen University, The Netherlands. He received Postdoctoral training at Oregon State University (1995-1999), the Free University of Amsterdam (1999-2000), and the Leibniz Institute for Plant Biochemistry, Halle/Saale, Germany (2000-2002). He is now an Associate Professor of Medicinal Chemistry in the College of Pharmacy and a Principal Investigator in the Linus Pauling Institute at Oregon State University. Mass spectrometry-based metabolomics is a new direction in his laboratory for discovery of biological effects of vitamins and phytochemicals.

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