# ABSTRACT


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| Charles University, Faculty of Pharmacy in Hradec Králové | |
| Training Workplace | Department of Biochemical Sciences |
| Doctoral Degree Program | Xenobiochemistry and Pathobiochemistry |
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| **Title of Doctoral Thesis** | Biotransformation of plant secondary metabolites and their modulatory effects on drug-metabolizing enzymes |



Sesquiterpenes and prenylflavonoids represent two classes of plant secondary metabolites that form an inherent part of human diet. They exert many beneficial biological activities, and accordingly, they are used as active constituents of herbal products. However, as xenobiotics, they also interact with a battery of drug-metabolizing enzymes and can in turn modulate their activity and/or expression, which may lead to herb-drug interactions. Sesquiterpenes and prenylflavonoids mentioned in this dissertation have been under-researched in this aspect.

Three acyclic sesquiterpenes (farnesol, cis-nerolidol, trans-nerolidol) and three cyclic sesquiterpenes (α-humulene, β-caryophyllene, β-caryophyllene oxide) activated gene transcription mediated by pregnane X receptor; however, they did not alter the mRNA or protein expression of their downstream targets, namely cytochrome P450 (CYP) 3A4 and CYP2C, neither did they affect the expression of the main hepatic carbonyl reducing enzymes.

Sesquiterpenes are substrates of drug-metabolizing enzymes which modify their structures in order to facilitate their excretion. In particular, a sesquiterpene lactone helenalin underwent two types of biotransformation reactions, oxidation and reduction. The former was catalyzed by a number of human CYP enzymes. Amongst them, CYP2A13 exhibited the highest efficiency, but it was in turn inactivated in a mechanism-based manner. In addition, a competitive inhibition of CYP3A4 by helenalin was also observed.

Intestinal drug-metabolizing enzymes are often neglected despite the fact that they largely contribute to the first-pass elimination of orally administered drugs and xenobiotics. Yet, prenylflavonoids xanthohumol, isoxanthohumol, 8-prenylnaringenin, and 6-prenylnaringenin significantly increased the activity of glutathione-S-transferase, catechol-O-methyltransferase, and the mRNA expression of uridine diphosphate-glucuronosyltransferase 1A6, while they decreased the activity of sulfotransferase. Collectively, we discovered that some of the studied compounds might pose a risk of provoking herb-drug interactions.