ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Biochemical Sciences

Bc. et Bc. Kristýna Deingruberová
Supervisor: doc. PharmDr. Iva Boušová, Ph.D.
Title of diploma thesis: Modulatory effect of *cis*-nerolidol, *trans*-nerolidol and farnesol on selected phase 1 drug-metabolizing enzymes in human liver slices

Sesquiterpenes are natural compounds which can be found in alternative medicines or food supplements. However, not all representatives have a beneficial effect on health. Indeed, sufficient attention should be paid to the evidence of serious toxicities and side effects. The aim of this diploma thesis was to find out, whether acyclic sesquiterpenes *cis*-nerolidol (cNER), *trans*-nerolidol (tNER) and farnesol (FAR) possess a modulatory effect on protein and gene expression of selected phase 1 drug-metabolizing enzymes - four cytochrome P450 (CYP) isoforms, namely CYP1A2, CYP2B6, CYP2C and CYP3A4, carbonyl reductase 1 (CBR1) and aldo-ketoreductase 1C3 (AKR1C3). The ultra-thin liver slices from five patients of both sexes aged 45 to 81 years were used as studied material. The liver slices were incubated with studied compounds at a concentration of 10 μM (in one patient, cNER and tNER also at 30 μM concentration) at 37 °C for 24 hours. The protein expression was determined by electrophoresis with Western blot and relative mRNA expression by quantitative polymerase chain reaction (qPCR).

The FAR and tNER at 10 μM concentration markedly inhibited CBR1 protein expression in the one patient. In other patient, cNER (10 and 30 μM) and tNER (30 μM) decreased AKR1C3 protein expression. The strongest effect on mRNA expression expressed tNER, which 2.1-times induced CYP1A2 expression in patient No. 9. Furthermore, FAR and tNER significantly reduced mRNA expression of all followed enzymes in one patient, at whom cNER at the same time significantly increased CYP2B6 mRNA expression. Beside inhibitory effects, FAR cause increase in CYP1A2 and CYP2B6 expression in two patients. The results pointed out interindividual variability among individuals. In conclusion, these acyclic sesquiterpenes at concentrations commonly available in the diet are unlikely to markedly affect the biotransformation of co-administered drugs.