ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Biochemical Sciences

Candidate: Mgr. Kateřina LNĚNIČKOVÁ

Supervisor: prof. Ing. Barbora SZOTÁKOVÁ, Ph.D.

Title of Doctoral Thesis:

MODULATION OF BIOTRANSFORMATION AND ANTIOXIDANT ENZYMES BY SELECTED NATURAL COMPOUNDS

Public interest in various dietary supplements containing herbs, herbal extracts or isolated active compounds has increased significantly over past decades. Consumption of these supplements increases worldwide and they are often consumed in unreasonably high doses, as they are generally considered as safe. Upon the intake to organism, these compounds are, as other xenobiotics, modified mostly by xenobiotic-metabolizing enzymes and they could influence these enzymes at the same time. Potential modulation of xenobiotic-metabolizing enzymes' activity (induction or inhibition) can seriously affect pharmacokinetics of concomitantly administered drugs. Knowledge of the possible impact of natural compounds on the xenobiotic-metabolizing enzymes is essential for their safe use.

The aim of this doctoral thesis was to study the effects of selected herbal extracts and their active chemical constituents on the activity and expression of xenobiotic-metabolizing and antioxidant enzymes. We have focused on the study of effects of American cranberry (*Vaccinium macrocarpon*, Ericaceae), green tea (*Camellia sinensis*, Theaceae) and Chinese bayberry (*Myrica rubra*, Myricaceae) extracts and their chemical constituents in the *in vitro* and the *in vivo* model systems. Green tea extract and its main catechin epigallocatechin gallate should not influence metabolism of co-administered drugs because their effect on the xenobiotic-metabolizing enzymes, which was studied *in vitro* in the intestinal cancer cell line Caco-2 in proliferative as well as in differentiated form (enterocyte-like cells), was only mild. Contrary, sesquiterpenes of Chinese bayberry caused significant cytochrome P450 inhibition *in vitro* in human and rat liver microsomes, but this effect was not confirmed in subsequent *in vivo* study in mouse liver and intestine. Administration of cranberry extract caused only moderate increase in xenobiotic-metabolizing enzymes' activity in rat liver, while

no changes in the activity of these enzymes were found in small intestine. Concomitant administration of cranberry extract should not cause serious drug interactions. Moreover, administration of cranberry extract to obese individuals could be beneficial, because its administration to mice with obesity positively influenced redox status and increased activity/expression of some antioxidant enzymes. Part of the experimental work was to evaluate time correlation between enzyme activity and its protein and gene expression upon induction. The intensity and time course of individual xenobiotic-metabolizing enzymes' modulation differed on individual levels as well as their correlation. Obtained results were useful for planning of subsequent *in vivo* studies.

The obtained results of this doctoral thesis extend the knowledge about acting of natural compounds on the organism. Revealing of the possible modulation effects of dietary supplements on the activity/expression of xenobiotic-metabolizing enzymes could contribute to the safe use of co-administered drugs.