Examiner's report on the doctoral (PhD) dissertation of MPharm N. Lekić: „Some aspects of molecular mechanisms of xenobiotics' hepatotoxicity and hepatoprotection: Modulatory roles of natural polyphenols

The presented doctoral (PhD) dissertation of MPharm Nataša Lekić: „Some aspects of molecular mechanisms of xenobiotics' hepatotoxicity and hepatoprotection: Modulatory roles of natural polyphenols" presents results of her PhD study in biomedicine in the area of pharmacology and toxicology . Her supervisor has been Prof. Dr. Hassan Farghali, DSc. The dissertation was elaborated in the Department of Pharmacology, First Faculty of Medicine, Charles University in Prague. The dissertation has 117 pages of typescript in English plus copies of 4 publications with IF (Impact Factor 1.55-2.0) published in 2011-2013 representing essentials of the dissertation where N. Lekić is twice given as a first author, twice as a co-author. This all is bound together in one volume. The 117 pages typesript includes Statement that this PhD Thesis has been written solely by N. Lekic and can be used for systematic electronic control of similarity of doctoral thesis, Acknowledgements, Abstract (in English and Czech), Table of contents, List of author's publications, List of abbreviations, Introduction (26 pages) with well written review of literature on the role of oxidative stress and apoptosis in hepatotoxicity, on pharmacological substances used (hepatotoxic D-galactosamine/lipopolysaccharide, tert-butyl hydroperoxide, hepatoprotective curcumin, quercetin), Research Aim & Hypothesis, Methods (13 pages), Results (28 pages), Discussion (14 pagers), Conclusion, Literature References (18 pages). The dissertation is supplemented with a separate PhD Thesis Summary (25 pages) with outline as above (required by the rules of doctoral studies in biomedicine in Czech Republic).

The dissertation is focused on an up-to-date topic – on finding early signal markers of hepatotoxicity at the gene level, on the study of relationship between conventional liver dysfunction markers and expressions of mRNA and proteins of important enzymes in

hepatotoxity produced by D-galactosamine/lipopolysaccharide, tert-butyl hydroperoxide. Furthemore, potential hepatoprotective effects of quercetin and curcumin were studied.

The presented dissertation has clearly formulated aims and hypotheses. Many up-to-date demanding methods had been used in this study (methods of biochemistry, molecular biology, histology, tissue cultures, experiments in rats – experimental therapy in vivo). Nataša Lekić thus could get a wide and good methodical skills and experience.

The dissertation is written in a very good English (as far as I can judge it), very carefully and rigorously.

The aims of the dissertation were fulfiled under rigorous conditions of scientific experiment.

Original results were obtained indicating the early activation of oxidative stress and apoptosis in the given hepatotoxicity models. Cytoprotective effects of quercetin appear to be mediated mainly by induction of the antioxidant enzyme heme oxigenase (HO-1), while curcumin was associated with the concomitant reduction of nitric oxide synthase NOS-2 and tumor necrosis factor-alpha (TNF-alpha) expressions.

I have no serious criticism to the methods, evaluation of results or other technical aspects of the dissertation. I have only a few questions, notes, which might be answered during disCussion at the thesis defence:

1. I wonder how far the profiles of hepatotoxic biochemical and molecular biological changes produced by the presently used model hepatotoxic substances (tert-butyl hydroperoxide, D-galactosamine/lipopolysaccharide) correspond to profiles of hepatotoxic changes produced by commonly used potentially hepatotoxic drugs such as paracetamol, nimesulide, valproate or others? Why these drugs are not used as model substances?

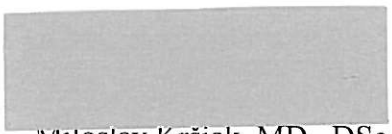
2. Quercetin or curcumin still do not have status of regular registered medicines, they are used as food additives . I have missed a more detailed assessment of their hepatoprotective effects found in other studies, by other authors in the dissertation.

3. You have found hepatoprotective effects in quercetin and curcumin in your studies. If their hepatoprotective effects should be tested in humans what dosage would be necessary? How big amount of curcumin, quercetin would be necessary to gain to start this testing (in humans)?

4. What are the threshold hepatoprotective doses of quercetin and curcumin in the present models of hepatotoxicity? Was there performed any pilot study to ascertain a dose-response relationship in this respect?

The dissertation presents original results, which N. Lekić published in full length in respected research journals with IF and with rigorous peer reviews.

In conclusion, I can state that the present PhD dissertation of Nataša Lekić completely fulfills requirements given in the rules for doctoral study programs in biomedicine namely that it is a self-contained scientific work with important and methodically properly obtained original results. The dissertaion gives evidence that MPharm Nataša Lekić is qualified for independent creative scientific work and to awarding her the title „PhD" (The required formulation in Czech: „Disertační práce prokazuje předpoklady MPharm Nataši Lekić k samostatné tvořivé vědecké práci a k udělení titulu „Ph.D." za jménem").



In Prague, 9th August 2013

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