

SCIENTIFIC OPINION

By

Assoc. Prof. Iliya Zhelev Slavov, Ph.D.

Department of Biology, Sector Pharmacognosy and Pharmaceutical Botany,
Faculty of Pharmacy, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna

By order N R-109-12, dated 21.01.2020 of the Rector of the Medical University of Varna, I was appointed to prepare an opinion on the procedure for obtaining a scientific degree "Doctor of Sciences" in the field of scientific education 7.0 Health and sports, professional direction 7.3. Pharmacy, specialty "Pharmacology (including Pharmacokinetics and Chemotherapy)" with a candidate Assoc. Prof. Kaloyan Dobrinov Georgiev from MU-Varna on the topic "Identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions".

Structure of the thesis

The dissertation submitted for defence is structured as separate chapters - 7 in total. It is written on 320 standard pages and its contents are illustrated with a total of 78 tables and 77 figures. The author has used 411 literary sources.

The urgency of the problem

The topic of the thesis is up-to-date, modern and innovative. Medicinal interactions in plant products are a serious problem because they contain many components and it is not always clear which one is responsible for the interactions. The difficulty of isolating individual compounds and determining the exact one which biological activity is due to is extremely laborious. Isolation of individual fractions helps to select compounds of similar structure that are thought to have similar biological activity.

General characteristics and contributions of the dissertation

The purpose and the 11 tasks set are correct and logical, which allows the implementation of the set ideas. The selected materials and methods, indicated in the separate chapters of the dissertation, allow solving the set tasks and achieving the scientific goal. Appropriate methods

for synthesis (of oligopeptides), isolation of plant fractions and analysis of biologically active substances have been used. In addition, the author has used numerous in vitro screening methods, in-silico simulation platforms to predict PK behavior and possible drug interactions of individual substances, studies in experimental animals (in vivo), as well as data processing from patient epicrisis and selection of a single population (in populo) to analyze potential drug-drug interactions. All this shows the variety of methods, which increases the value of the thesis. The results and proposed discussions in the individual chapters are understandably presented and illustrated with the tables, figures and equations that are adequately used. The main contributions and importance of development to science and practice can be summarized as follows:

- Screened for inhibition of *CYP3A4* and *CYP2C9* (major cytochrome isoforms associated with drug interactions), multiple plant fractions and oligopeptide compounds.
- The algorithms proposed by the Regulatory Agencies for evaluating the risk of drug interactions for substances with proven inhibitory properties on cytochrome enzymes are monitored and the individual methods are evaluated.
- From the pharmacodynamic point of view, the combinational effects of the fractions isolated from *Bancho*, *Pu-erh* and *L. barbarum* with doxorubicin on breast cancer cell lines were determined, as well as the ability of these fractions to protect the main dose-limiting effects (cardio - and nephrotoxicity) from the use of doxorubicin in rats.
- The risk factors leading to an increased incidence of drug interactions in heart failure patients have been identified and recommendations have been made to reduce their frequency.

I fully agree and accept all the conclusions and contributions that the author has provided.

The presented abstract is prepared according to the requirements, very well structured and fully reflects the content of the dissertation. Absolutely all of the author's own results are included.

The actual publications, presented by Assoc. Prof. Georgiev, which have not been used in other competitions, are in accordance with the requirements of the Rules for the development of the academic staff at the Medical University Varna. All publications are related and cover a large part of the topics in the dissertation and the results achieved at the various stages of the

development of scientific work. In ten of the publications the dissertant is the first author, in one he is the third co-author, which shows that the ideas and the way of presentation are the main merit of the dissertant.

Remarks

It is noted that only one source is in Cyrillic and the rest is in Latin. In fact, the author has omitted to mention that there are three more sources in Cyrillic - articles from the Russian Pharmacopoeia.

Conclusion

The dissertation work of Assoc. Prof. Georgiev "Identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions" is up-to-date and meets the scientometric criteria laid down in the Law on Development of the Academic Staff in the Republic of Bulgaria (ZRARB), the Regulations for the Implementation of the Act, as well as and the Rules for Academic Development of MU - Varna for the degree "Doctor of Science". The work helps to expand knowledge of drug interactions, with an emphasis on those related to the use of herbal products.

Because of the above I recommend the Honorable Members of the Scientific Jury to vote positively for the degree "Doctor of Science" in Pharmacology to Assoc. Prof. Kaloyan Dobrinov Georgiev, Ph.D.

17.02.2020

Varna

Signature:



/Assoc.Prof. Iliya Slavov, PhD/