MEDICAL UNIVERSITY-SOFIA, FACULTY OF PHARMACY, DEPARTMENT OF PHARMACOLOGY, PHARMACOTHERAPY AND TOXICOLOGY

SCIENTIFIC OPPINION

Prepared by Prof. Virginia Yordanova Tzankova, PhD, ERT, Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University, Sofia, nominated as a member of the Scientific Jury with Ordinance No. R-109-12 / 01/21/2020

Subject: Thesis for the degree of **Doctor of Science** in: 7.0 Health and sports, professional direction 7.3. Pharmacology, section "Pharmacology (including pharmacokinetics and chemotherapy

Author: Assoc. prof. Kaloyan Dobrinov Georgiev, Mpharm, Ph.D.
Thesis: "Identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions"

The opinion has been prepared in accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for its implementation at the Medical University – Varna.

Short CVs

Kaloyan Dobrinov Georgiev was born in 1978 in Varna. In 2003 he was graduated from Faculty of Pharmacy, Medical University - Sofia (educational degree Master in Pharmacy; diploma thesis on "Potentiation of the antileukemic effects of bendamustin in combination with imatinib and erufosine"). In 2005, Mr. K. Georgiev was appointed as an assistant professor in Medical University-Varna. In 2013, he successfully defended his PhD thesis on „Design, Synthesis and Pharmacological Characterization of Peptide Mimetics of Endomorphine -2, morphiceptin and RGD with analgesic and anti-inflammatory activity". Dr. Kaloyan Georgiev has obtained two postmaster specialties in Pharmacology and in Clinical Pharmacy, acquired in 2010 and 2018 respectively. From 2015 up to now he is an Associate

Professor in Pharmacology. Currently, he is appointed as a Head of the Department of Pharmaceutical Technologies at the Faculty of Pharmacy in the Medical University – Varna.

Importance of the problem

Safe drug therapy is one of the main responsibilities of healthcare professional providers. Patient's therapy often involves the use of concomitant administration of two or more drugs that may interact and consequently - could cause serious side effects. Recently, a lot of data on potential drug interactions and their negative consequences have been reported in the scientific literature. The increased information on potential drug interactions became a significant problem for healthcare professionals, because of unclear underlying mechanisms or missed evidences for significant clinical relevance. Another important concern in the modern pharmacotherapy is the concomitant use of conventional drugs with herbal supplements. These combinations are often considered as safe, but their possible interactions are still not well understood.

The proposed doctoral thesis represents a complex study on drug-drug interactions with substances from natural or synthetic origin (oligopeptides), evaluated by using a battery of in silico, in vitro and in vivo methodological approaches.

The doctoral thesis is written on 320 pages. It is structurally divided in 7 main sections, conclusions, references, list of publications related to the dissertation and relevant Annexes. The references are precisely chosen and show high level of awareness of the problem. They include 441 titles, the majority of them being published in recent years. The structure and layout of the dissertation are in line with the institutional requirements, and shows a good technical performance.

Overview of the scientific literature

The scientific overview addresses the main thematic issues which are relevant to the aim and subjects of the proposed research. The information is logically and consistently presented; it is related to the assigned tasks and purpose of the study. An overview of the most widely used methods of analysis and evaluation of drug interactions is carried out.

The scientific overview is based on evaluation of a great number of literature sources, most of which were published recently. This supports the importance of the

mentioned topic. The proposed scientific overview is well presented and summarized, thus showing that Assoc. Prof. K. Georgiev possess a good knowledge on the problem, its logical arrangement and motivation of the topic of the study.

Purpose, assignments, hypotheses and research methods. Compliance of the research methodology with the purpose and tasks of dissertation

The logic scientific hypothesis is formulated, based on the scientific literature overview. The **objectives and** the tasks are described clearly and precisely. The selected methodological diversity guarantees a successful implementation of the assigned tasks. A wide range of methods and models are proposed and used in the study, which allows a complex assessments and evaluations. Among the methods used, we can mention an isolation and analysis of biologically active substances (BAS) from natural products; synthesis and analysis of oligopeptides; determination of the inhibitory potential of BAS on some of the most important CYP450 isoenzymes (CYP3A4 and CYP2C9). A very good impression gives the performed complex risk assessment of drug interactions. It includes a battery of *in silico* methods (generation of physical-chemical and pharmacokinetic data by using swissADME and pkCSM software, simulation of possible interactions with ADMEWORKS DDI and SimCYP programs, *in vitro* methods (determination of different markers on human tumor and non-tumor cell lines); *in vivo* pathological models of induced nephrotoxicity and cardiotoxicity in rats, as well as determination of the risk factors for drug interactions in clinics, by using an appropriate software. Statistical analysis was performed by careful selection of an adequate statistical methods, allowing good interpretation of the obtained results.

I believe that the proposed experimental methods (in silico, in vitro and in vivo) are appropriately selected, sufficiently informative and allow adequate scientific research for solving the aim and task of the study. The presented experimental methodological protocols show a good ability of the author to interpret the obtained results.

Presentation of the scientific results

The scientific results are presented in sections III – VII of the thesis. Section III (*Selection, isolation and analysis of plant extracts/fractions. Design, synthesis and*

combination of the natural extracts/ isolated fractions of *L. Barbarium* with doxorubicin shows protective effects against doxorubicin-induced cardio- and nephrotoxicity in animal models in *vivo*. **Section VI** presents the results of risk assessment for potential clinical drug interactions in adult patients with heart failure. The effects of drug therapy (drugs with narrow therapeutic index, such as statins, anticoagulants, antiplatelet agents, cardiac glycosides) were evaluated, using Lexicomp® Drug Interactions data base. A good correlation between ADR frequency and the treatments with drugs with narrow therapeutic index, as well as polypharmacy and patient's multiple morbidity was established and reported.

Section VII summarizes the role of computerized systems in improving the identification, analysis and evaluation of drug interactions in both pre-clinical and clinical stages of drug development. The role of sophisticated software products for the timely detection and analysis of potential adverse drug interactions is underlined. This approach increases the predictability, foreseeability and prevention of drug interactions as an important step towards a safe pharmacotherapy.

The valuable discussions are made after each relevant section of the dissertation. The results are logically summarized and discussed by the author. The conclusions are clearly written and reflect correctly to the main scientific purpose and tasks of the work.

Main contributions

The original and scientific applied contributions are summarized. The original contributions are pharmacokinetic and pharmacodynamic characterization of methylxanthine fraction of the leaf of Bancha and Pu-er, isolated fractions and total extract of *L. Barbarum*, as well as newly synthetized oligopeptide analogues of endomorphine-2. The inhibitory potential of different fraction of *L. Barbarum* on the CYP3A4 and CYP2C9 isoenzymes have been demonstrated. Scientific applied contributions are the proposed guidelines for pharmacokinetic simulation and assessment of pharmacokinetic drug interactions; valuable recommendations for using an appropriate software product for detection and analysis of potential drug interactions by clinical pharmacists. The thesis emphasizes the important role of the clinical pharmacist in the multidisciplinary clinical teams. This approach will assure safe and effective pharmacotherapy, especially in high-risk patients.

I accept the contributions of dissertation as they are properly described, precisely defined and justified.

Notes and reccomendations

In generally, the thesis is well written. Therefore, I have some non-essential remarks related to the correctness of the used terminology. I recommend using the medical terminology, as defined by the national law (National Drug Act) and corresponding regulations (e.g. the term "preparations" (table 13 of results) is more correct to be replace with „drug product/formulation", or if applicable with the term „active substance"). Having in mind the interesting findings, reported in sections III to V, I would recommend further in-depth study of potential adverse effects/ drug interactions in oncology patients treated with doxorubicin (for both hematological and solid tumors). Adjuvant therapy often includes dietary supplements of plant origin (incl. polyphenolic compounds with proven antioxidant activity). In this regard, some future studies on possible drug interactions, using the methodology developed in this dissertation would be of great benefit to the clinical practice.

Publications

The author presents 19 publications, eleven of which were not used in previous contests., Assoc. Prof. Georgiev is the first author in 16 publications, in 2 publication he is the second author, which clearly shows his main contribution to the presented works. Seven articles are published in peer reviewed and indexed journals, and two of the publications are listed in journals with an impact factor; 33 scientific citations are reported.

The authors publications reflect to the aim and tasks of the dissertation. The presented data covers the criteria for acquiring the scientific degree "Doctor of Sciences", and the rules for the development of academic staff in MU-Varna.

Conclusion

The doctoral thesis on the topic: "identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions" presented by Assoc. Prof. Kaloyan Georgiev, PhD, is an original and in deep performed scientific work. It

represents a high level study, performed by using complex methodological approaches; the reported results critically and thoroughly are discussed.

Based on the above-mentioned conclusions, I believe that the scientific work performed by assoc. prof. K Georgiev meets the requirements of the national law (ZRASRB) and the corresponding rules of Medical university-Varna for its application, which gives me a reason to vote with POSITIVE mark.

I encourage the honorable scientific jury to vote positively and to award Assoc. Prof. Kaloyan Georgiev, PhD the scientific degree "DOCTOR OF SCIENCE" in the field of higher education 7.0 Health and sport, professional direction 7.3. Pharmacy, Scientific Specialty "Pharmacology (incl. (Pharmacokinetic and Chemotherapy) ".

15. 02. 2020 г.
Sofia

Signature:

/Prof. V. Tzankova, PhD, ERT/