REVIEW

Of dissertation on the topic "Identification, analysis and evaluation of pharmacokinetic and pharmacodynamic drug interactions" for the degree "Doctor of Science" in 7.0 Health and sports, professional field 7.3. Pharmacy, specialty "Pharmacology (including pharmacokinetics and chemotherapy)"

Author: Assoc. Prof. Kaloyan Dobrinov Georgiev PhD, Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy, Medical University Varna

Reviewer: Prof. Dr. Mila Vlaskovska, MD, PhD, DSc, Faculty of Medicine, Medical University of Sofia

Business address: Art. Cor. Prof. Dr. Mila Vlaskovska, MD, MD
Department of Pharmacology and Toxicology
Faculty of Medicine, Medical University of Sofia
2, Zdrave Str., 1431 Sofia
e-mail: mvlaskovska7@gmail.com; mvlaskovska@medfac.mu-sofia.bg

I was elected as a reviewer of the submitted thesis on January 21, 2020 by Order No. P-109-12 of the Rector of MU-Varna.

I did not find any gaps in the documentation provided by Assoc. Prof. Kaloyan Dobrinov Georgiev. I declare that I have no common scientific works with Assoc. Prof. Georgiev.

DATA FROM THE PROFESSIONAL BIOGRAPHY

Kaloyan Dobrinov Georgiev was born in 1978 in Varna.

2003 – He has graduated from the Faculty of Pharmacy, Sofia with a diploma in pharmacology "Potentiation of the antileukemic effects of bendamustin in combination with imatinib and erufosine".

2005 – He has won an assistant competition and was appointed to the Department of Pharmacology at the Medical University of Varna.

2010 - Kaloyan Georgiev is admitted as a PhD student in the section "Pharmaceutical design and biochemical pharmacology" at the Bulgarian Academy of Sciences (BAS) Sofia.

2013 – Successfully defended his dissertation "Design, synthesis and pharmacological characterization of endomorphin-2, morphiceptin and RGD peptide mimetics with analgesic and anti-inflammatory activity".

2010 - Acquires specialty Pharmacology

2018 - Acquires Clinical Pharmacy Specialty

From 2015 until now, he holds the academic position of Associate Professor.

He is the head of the Department of Pharmaceutical Technologies at the Faculty of Pharmacy, Medical University - Varna.

ASSESSMENT OF THE DISSERTATION WORK SUBMITTED

The actuality of the problem

Nowadays, medical practice is accompanied by massive prescribing and non-prescription use of a large number of pharmacotherapeutic products as well as nutritional supplements. The issue of reporting and monitoring of adverse reactions and drug/nutritional interactions becomes more and more important. The responsibility of all physicians and clinical pharmacists is to inform National drug agencies and EMA.

The dissertation presented is up-to-date, because due to the wide range of methods and new computer and software technologies it develops and offers optimization of the prediction of risks of drug interactions, as well as interactions with nutritional supplements or active ingredients of plant products.

Although at first glance the dissertation may seem fragmented - the 5 major chapters summarize the most basic research and the resulting contributions, it should be noted that this systematic approach helps the author to combine perfectly researches on different drug groups and synthetic and/or ingredients isolated from plant sources on major socially significant nosological units such as malignancies, cardiovascular disease and pain symptoms. A great advantage of the dissertation is the skillful combination of research in fundamental pharmacology with high-tech chemical analysis and synthesis and clinical pharmacology with pharmacokinetics. I particularly appreciate the combination of these approaches with modern computer programs for the analysis and prediction of drug and other interactions. The studies that have been analyzed with state-of-

the-art programs are essential from the perspective of evaluation of drug interactions, especially in the field of cardiovascular and cancer diseases.

Conclusions and scientific contributions

The conclusions reached by the author are a logical consequence of competent data analysis. The most significant conclusions and contributions of the dissertation are formulated on the basis of many experimental studies combined with computerized simulation methods and can be summarized as follows:

1. Complex characterization of pharmacokinetic interactions of isolated methylxanthine fractions from *Bancha* and *Pu-erh* tea leaves, isolated fractions (polysaccharide, pectin-free and total extract) from *L. barbarum* (Goji berry) and newly synthesized endomorphin-2 oligopeptide analogues with respect to *CYP3A4* and *CYP2C9* isoenzymes.
2. PBPK models of plant fractions with proven major components as well as newly synthesized oligopeptides based on in silico data were prepared and simulations for possible drug interactions with *CYP3A4* substrates were performed.
3. The individual algorithms and models for tracking proven enzyme inhibition in the development of new drugs have been evaluated, as well as the individual simulation programs were used to evaluate drug interactions.
4. The anti-proliferative effects of methylxanthine fractions isolated from *Bancha*, *Pu-erh* and *L. barbarum* fractions on breast cancer tumor cell lines were determined. Their effect in combination with doxorubicin has been determined in two aspects: increased therapeutic efficacy and reduced organ toxicity.
5. To reduce the risk of potential drug interactions in adult patients with cardiovascular disease, appropriate software should be used to analyze the prescribed therapy and it is necessary to include a clinical pharmacist in the multidisciplinary team.

A significant part of the results of the studies conducted are original, the scientific contributions have both significant theoretical and practical value and the conclusions are convincing.

Scientific hypothesis, purpose, tasks, literary review and structure of the dissertation

The scientific hypothesis of the dissertation focuses on the need for a methodological set to prove drug interactions with active and inactive constituents from plant sources, including newly

synthesized analogues. The results of this approach are the prediction of adverse reactions and the optimization of pharmacotherapy.

The aim of the dissertation is to study, analyze and evaluate drug interactions at the pharmacodynamic and pharmacokinetic level by applying *in vitro*, *in vivo* and *in populo* data processed with modern and internationally acknowledge software platforms (in silico). The 11 tasks have been formulated clearly and they follow the substantive structure of the dissertation and help to accomplish the goal.

I would like to express my appreciation for the analytical approach and the ability of Assoc. Prof. Georgiev to combine logically different methodology and character results, some of which are fragments of studies for the acquisition of a doctoral thesis. As will be noted in characterizing the structure of the dissertation, it consists of 7 chapters with a brief overview, methodology, results and discussion.

The literary review of the entire dissertation is presented on 49 pages with 124 references. The basic terms and concepts used in the description of drug interactions are competently and understandably presented and examples of pharmacokinetic and pharmacodynamic drug interactions are discussed.

The main chapters of the dissertation are as follows

In **Chapter III**, "Selection, Isolation and Analysis of Plant Extracts and Fractions", are used plants suspected to cause drug interactions. Specific fractions, for which there is no evidence of their involvement in drug interactions, has been isolated and analyzed.

Chapter IV, Pharmacokinetic Drug Interaction Studies, is naturally the most voluminous part of the dissertation (101 pages in total and 97 in literature). Assoc. Prof. K. Georgiev demonstrates proficiency in in vitro screening techniques for newly isolated plant fractions and oligopeptides using vivid kits for possible inhibition of the two major cytochrome isoforms – *CYP3A4* and *CYP2C9*, their IC_{50} values, the mechanism of inhibition and their inhibitory constants (Ki) are determined. Then, using common algorithms from executive agencies (such as the FDA, EMA, etc.) – basic and mechanistic (static and dynamic) models, the whole pathway to characterize a substance, with proven inhibition of a drug-metabolizing enzyme, was traced determining its potential to induce drug interactions in clinical situations. The author applies a physiology-based

pharmacokinetic model (PBPK) to prepare a pharmacokinetic profile through the *SimCYP* and *ADMEWORKS DDI* platforms of the methylxanthine fraction and oligopeptides. Highly appreciated is the skillful use of software, which is a sophisticated computer platform, used by leading pharmaceutical companies (for example, *SimCYP* is in the top 10 in the world). For me, even more appreciated is the fact that Assoc. Prof. Georgiev implements and uses successfully the abilities gained during his specialization at *Certara*® (holding the rights to *SimCYP*).

I cannot hide my sincere affinity for Assoc. Prof. Kaloyan Georgiev (I saw him once, but it is on the basis of the biography and dissertation presented) for his continuous pursuit of new knowledge and upgrading in a methodological and theoretical plan, combined with enduring energy for effective dreams realization and translating results to optimize pharmacotherapeutic practice.

Chapter V, 'Pharmacodynamic Drug Interactions', plant-derived fractions (Bancha, Pu-erh and L.barbarum) have been tested on breast cancer cells *in vitro* and the efficacy and reduction of adverse reactions in combination with doxorubicin. Overall, it is worth noting that the search for approaches to reduce the toxicity of doxorubicin to non-tumor tissues and cells remains an urgent problem.

Chapter VI "Study and analysis of pharmacokinetic and pharmacodynamic drug interactions in clinical practice" The main potential drug interactions (pDDIs) in patients with heart failure with Lexicomp® Drug interactions have been identified and analyzed - one of the most commonly used methods in clinical drug evaluation interaction. The *SimCYP* simulator was also used to analyze the pharmacokinetic interactions associated with *CYP2C9*, *CYP3A4* and *P-gp*. The risk factors that lead to an increase in the frequency of drug interactions with adverse effects on the patient have been identified. Attention is drawn to the need to introduce clinical pharmacists into clinical practice, especially in high-risk patients.

Publications related to the dissertation

The author presents 19 publications, eight of which have been used in previous competitions and eleven that have not been used. In 16 of them, Assoc. Prof. Georgiev is the first author, in 2 - second author and in 1 - third author, which clearly shows the main contribution of the author in the presented works. Two of the publications are in Impact Factor journals - 4.011 (Scientific reports) and 1.69 (International journal of clinical pharmacy).

Part of the dissertation work was funded by a project from the Science Foundation 2016 at the Medical University of Varna - "Study of drug interactions at the level of biotransformation".

Critical notes and recommendations

The literature review of some of the figures and tables does not indicate the sources from which the information was obtained. In Chapter IV "Pharmacokinetic Drug Interactions", there are figures that are not translated into Bulgarian. It is not clear why the author has chosen these two software platforms to evaluate pharmacokinetic interactions. The scientific forums in which the dissertation data were reported are not indicated.

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 scientific criteria, as well as the rules for academic development of the Medical University - Varna for the scientific degree "Doctor of Sciences".

Based on the positive aspects of the dissertation presented, I recommend the Honorable members of the Scientific Jury to vote positively for the degree "Doctor of Science" in Pharmacology to the Associate Professor Kaloyan Dobrinov Georgiev, PhD.

17/02/2020 Reviewer:

Sofia /Prof. Dr. Mila Vlaskovska, MD, PhD, DSc/