

SCIENTIFIC OPINION

From

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Member of the scientific jury on the basis of order R-109-92 / 24.02.2022 of the Rector of the Medical University of Varna and appointed to prepare an opinion according to protocol 1 / 09.03.2022.

SUBJECT: Public defense of the dissertation of Assis. Prof. Maya Petrova Radeva-Ilieva for obtaining the educational and scientific degree "Doctor" in the field of higher education 7. Health and Sports, 7.3. Pharmacy and doctoral program "Pharmacology (including pharmacokinetics and chemotherapy)" with the thesis: "Isolation and analysis of methylxanthine fraction, catechin fraction and total extract of Bancha green tea and study of their effect on the pharmacokinetics of sildenafil in rats."

Scientific supervisor of the dissertation is: Assoc. Prof. Kaloyan Dobrinov Georgiev, Ph.D.

Relevance of the dissertation

The dissertation covers a very current issue, namely the risk of potential drug interactions of medications with simultaneous intake of foods, supplements and herbal drugs. Green tea is one of the most widely used beverages in the world, also available in the form of many nutritional supplements containing individual components or the overall rich composition of biologically active substances recommended for a variety of diseases or physiological conditions. All of these components have complex pharmacokinetics, including modulation of multiple cytochrome enzymes and transport proteins, which determine a high risk of potential drug interactions.

The literature review in the dissertation is very well structured and presents current data of the problem with green tea and other food supplements and herbal drugs. It is noteworthy that the author has used mainly literature sources, referenced and indexed in the largest databases

published in the last five years, which confirms the relevance of the topic and shows her ability to summarize currently available information on a given issue.

Purpose, tasks and materials and methods used

The aim of the dissertation is clearly defined, namely to evaluate the influence of the individual fractions - catechin, methylxanthine and whole extract isolated from Banacha green tea on the pharmacokinetic behavior of sildenafil.

The main tasks that are set in the dissertation are six, as they follow the initially set goals and could be summarized as follows:

- Isolation of Banacha green tea fractions
- Analysis of the main phytochemical components in fractions
- Monitoring of changes in plasma concentrations of sildenafil in rats when co-administered (in some of them after a single dose, in others after multiple administration)
- Statistical processing of the obtained results

The dissertation is also enriched and fortified with the construction of a PBPK model and simulation of these interactions in humans, as a possible initial screening to serve for further development.

The richness of the materials and methods used in the dissertation is impressive. The candidate shows knowledge in the fields of phytochemistry and analysis and in the design of research on experimental animals and the handling of modern, high-tech software used in the construction of PBPK models as well. Of high importance for the acquisition of this scientific title is the mastery of the largest possible set of methodologies that are combined and contribute to the proof of a thesis as a whole.

Results, conclusions and contributions

The results and conclusions presented in the dissertation show that the simultaneous use of individual components or fractions of them, as well as the whole extract of green tea Banacha, may affect the pharmacokinetics of drugs undergoing biotransformation of CYP3A4. In this case, this is illustrated by the use of sildenafil, which is mainly eliminated this way. Consequently all drugs eliminated this way (nearly 40% of the drugs used) can be affected of the simultaneous use of green tea Banacha. Therefore it is necessary to consult a specialist in the field of drug interactions and monitor patients taking drugs that are substrates of CYP3A4 before prescribing or recommending green tea (due to the many proven benefits for human health).

Eight contributions of original, scientifically applied and confirmatory nature have been presented, which are very well outlined and stand out when reading the dissertation.

Publishing activity

The dissertation has presented three publications in connection with the dissertation, two of which are in international journals with an impact factor, which significantly exceeds the requirements. The publication in the DARU Journal of Pharmaceutical Science (IF = 3.117) is impressive and it covers the main material presented in the dissertation. This shows that a large part of the presented work has earned an international independent evaluation and received the well-deserved recognition. It should also be emphasized that the dissertation is supported by two projects at national level.

Conclusion

The dissertation covers an up-to-date topic and manages to combine the application of knowledge from basic, experimental and clinical pharmacology, as well as from pharmaceutical fields, such as pharmacognosy, phytochemistry and pharmaceutical analysis. It fully complies with the Law on the Development of the Academic Staff in the Republic of Bulgaria, both the Regulations for its implementation and the Regulations of Medical University of Varna for the acquisition of scientific degree "Doctor".

Above mentioned gives me a reason to give a **POSITIVE EVALUATION** and to offer the esteemed members of the Scientific Jury to vote for the award of educational and scientific degree "Doctor" in the field of higher education. 7. Health and sports, professional field 7.3. Pharmacy and scientific specialty "Pharmacology (including pharmacokinetics and chemotherapy)" to Assis. Prof. Maya Petrova Radeva-Ilieva.

Varna, 11.04.2022

Signature:.....

/Assos. Prof. Iliya Zhelev Slavov, PhD/