STATEMENT

by assoc. prof. Dr. Maria D. Zhelyazkova-Savova, MD,

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About dissertation work on:

PHARMACOLOGICAL STUDY OF THE EFFECTS OF CHAENOMELES MAULEI FRUIT JUICE IN AN EXPERIMENTAL MODEL OF METABOLIC SYNDROME

For awarding the educational and scientific degree "DOCTOR"

To a doctoral student in an independent form of study

Klementina Moncheva Moneva-Marinova

by field of higher education 7. Healthcare and sports, professional direction 7.1. Medicine, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)"

Based on order No. P-109-46/29.01.2024 of the Rector of MU-Varna and by the decision of a meeting of the Faculty Council of the Faculty of Medicine at MU-Varna (protocol No. 16/07.02.2024), I am designated as a member of the Scientific Jury and as such I present my opinion regarding the doctoral thesis of Dr. Klementina Moncheva Moneva-Marinova on the topic ***"Pharmacological study of the effects of Chaenomeles maulei fruit juice in an experimental model of metabolic syndrome"***

The set of materials presented to me on an electronic device includes all the necessary documents in accordance with the requirements of the Law on the Development of the Academic Staff and the Regulations on the Development of the Academic Staff of MU-Varna.

Education and professional path of the dissertation student

Klementina Moneva completed her secondary education in 2012 at the Foreign Language High School Romain Rolland in Stara Zagora, majoring in English and German. She received her medical education at Varna Medical University, graduating in 2018. Immediately thereafter (2018), she joined the Department of Pharmacology and Clinical Pharmacology and Therapy, MU Varna - initially as a part-time and then as a full-time assistant, where she still works today. She conducts seminars with students from the Bulgarian- and English-language programs – in pharmacology and clinical pharmacology. Dr Moneva speaks English and German – at a high and medium level, respectively. She is a member of the Bulgarian Society of Pharmacology and Clinical Pharmacology and Therapeutics and the European Association of Clinical Pharmacology and Therapeutics.

Relevance of the topic

Metabolic syndrome (MS) is a current problem for modern medicine, given its wide distribution, affecting all age groups (including children) and its role as a risk factor for many socially significant diseases – metabolic, cardiovas cular, hepatic, neuro-psychiatric. Despite

the fact that today much is known about its pathogenesis, prevention and treatment of MS are still far from optimal.

Dissertation review and analysis of results

Dissertation structure

The structure of the work is well balanced. The dissertation is written on 124 pages. It is built in accordance with the adopted standards and includes the following sections: Introduction – 3 pages; Literature review – 28 pages; Aim and tasks – 2 pages; Material and methods – 7 pages; Own results with discussion – 50 pages; Summary discussion – 4 pages; Conclusions – 4 pages; Contributions – 2 pages; List of publications and participations – 2 pages; References (186 sources in English) – 15 pages.

Knowing the problem

The PhD student shows a very good literary awareness regarding the problems raised in the disertation. She works freely with literature sources, demonstrating skills in analysis and interpretation. It is noteworthy that almost 50% of the cited data are from the last 5 years. The overview is presented in three parts. The first one concerns the MS. It is concisely described and yet the main pathogenetic mechanisms that can be pharmacological targets are pointed out. Along with the well-known classical factors for the development of MS, there are also those that have been the subject of more recent attention, such as circadian rhythms in nutrition and physical activity, the role of the gut microbiome, and sympathetic overactivity. The possibilities for experimental modeling of MS and the relevance of different models to human pathology are also discussed. The second part deals with the botanical characteristics of the Japanese quince, the chemical composition of the juice, as well as the data known so far from experimental studies in vitro and in vivo. The third part is dedicated to the effects of the polyphenols known to be present in the studied juice, on MS. They are discussed briefly and to the point, without unnecessary details.

The objective of the dissertation is logically deduced from what is already known about the Chaenomeles maulei fruit juice (CMFJ), and the polyphenols contained in it. The tasks to achieve the set goal are clearly and precisely formulated.

Methods used and design of experiments

50 male white Wistar rats, divided into 5 groups of 10 animals, were used in the dissertation work. The various methods used are adequate to the tasks set. Biochemical, behavioral, somatic and histopathological indicators were investigated to evaluate the action of Chaenomeles maulei fruit juice (CMFJ) in a diet-induced model of MS. Among the criteria for assessing the carbohydrate status, the innovative marker for insulin resistance – TyG index, has been introduced. The experiment was chronic, the animals were treated for 10 weeks with 3 different doses of CMFJ, and the results were compared with those of untreated MS rats and pure controls. One-way ANOVA and Student's t-test were used for statistical analysis of the results.

Analysis and evaluation of results

The results are consistently reported in several sections, following the execution of the tasks, and accompanied by a discussion; they are illustrated with a total of 13 tables and 22 figures.

Dr. Moneva's work confirms the appropriateness of the used MS model as adequate for reproducing human metabolic pathology and associated cardiovascular, hepatic, and neuropsychiatric impairments.

Several significant effects of the CMFJ in MS stand out – reduction of adipose tissue index (total, as well as mesenteric and paranephric), dose-dependent reduction of the oxidative stress marker TBARS, beneficial effect on the histological manifestations of MS in the myocardium and vascular endothelium, fat and liver tissue. An anxiolytic effect was also observed in the elevated plus-maze test, although the dietary challenge alone did not induce a significant change.

Other indicators showed favorable trends in influencing the manifestations of MS: a decrease in TG in the smallest dose of CMFJ, increased antioxidant protection in doses of 2.5 and 5 ml, a decrease in liver index, and an improvement in spatial memory.

The dissertation's strongest point is the thorough and competent discussion – both sectionally and in summary. The work is intelligently written, the language of the exposition is excellent, the statement is clear and precise, the thought is smooth and logical. Good literature knowledge allows the author to interpret the data from different perspectives, looking for and finding suitable mechanisms to explain the effects, or lack thereof. Yet, at times the clear connection between the observed effects and the actions of polyphenols cited in the literature (e.g. their influence on satiety, or their role in the "browning" of the white adipose tissue) is not easy to follow.

Conclusions and contributions

I accept the conclusions thus formulated and the original nature of the contributions. I would like to point out that, in генерал, the author correctly distinguishes the apparent effects from the observed trends. Sometimes, however, unjustifiably categorical statements are made which could be replaced by a more objective presentation of the results.

Publication activity

Dr. Moneva has presented 4 published articles on the topic of the dissertation (one of which in a journal with an impact factor) and two participations in scientific forums at home and abroad.

Among the publications, I would like to share my satisfaction with the review article "Mimetics of caloric restriction as a therapeutic approach in metabolic syndrome". This topic has recently attracted considerable scientific interest and is widely discussed in the literature. Similar to the benefits of caloric restriction, some well-known drugs, as well as various natural products, show the potential to beneficially affect age-related pathologies, and thus emerge as promising anti-aging agents. The article focuses on polyphenols as mimetics of caloric restriction in MS with an emphasis on possible mechanisms of action. The review is closely related to the problems set in the PhD work and the discussion of the results.

Evaluation of the abstract

The abstract, written on 80 pages, meets the requirements of the regulatory framework and correctly reflects the content of the dissertation work.

Personal impressions of the candidate

I know Klementina Moneva as a modest, intelligent, smiling young person. She is a hard-working and a dedicated researcher, sparing no time and effort. She also puts a lot of diligence and serious preparation into her work with the students, for whom she is a loved and respected teacher. For the team in the department and for her colleagues, she is also a welcome and radiant friend and interlocutor.

Conclusion

The PhD thesis of Dr. Klementina Moneva represents a serious experimental work on an actual health problem with interesting results that can be useful for practice. With the favorable effects that CMFJ has shown in the model of metabolic syndrome, it may be tested clinically as a functional food. The author demonstrates an ability to work independently, analyze, interpret, and summarize results, formulate clear and accurate reasoning, and derive conclusions. The publication activity satisfies the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff at the MU-Varna for awarding the scientific and educational degree "DOCTOR". With these grounds, I present my positive assessment and vote with conviction FOR awarding the scientific and educational degree "DOCTOR" to Dr. Klementina Moneva-Marinova.

Prepared by:

/ Assoc. Prof. Maria Zhelyazkova-Savova, MD/

5.04.2024

Varna