

OPINION

by **Prof. Tania Koleva Pencheva, PhD**

Institute of Biophysics and Biomedical Engineering –
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Regarding a procedure of promotion to the **educational and scientific degree “Doctor of Philosophy”**

Area of Higher Education: **4. Natural Sciences, Mathematics and Informatics**

Professional Field: **4.3. Biological Sciences**

Doctoral Programme: **Application of the Principles and Methods of Cybernetics
to the field of structure – activity relationships of biologically active substances**

Author of the dissertation thesis: **Antonia Georgieva Diukendjieva-Todorova**

Title: ***“In silico and in vitro Studies of ADME/Tox Properties and Molecular Interactions of
Flavonolignans from Silybum Marianum L.”***

According to Order No. 707/11.09.2023 of the Director of the Institute of Biophysics and Biomedical Engineering (IBPhBME) at the Bulgarian Academy of Sciences, I was appointed member of the Scientific Jury for the defence of the dissertation thesis by the PhD student **Antonia Georgieva Diukendjieva-Todorova** for the acquisition of the educational and scientific degree “Doctor of Philosophy”.

As a member of the Scientific Jury, I have been provided with:

1. A dissertation thesis for acquisition of the educational and scientific degree “Doctor of Philosophy”.
2. A synopsis of the dissertation thesis.
3. Copies of the publications which the thesis is based on.
4. Other procedure-related documents.

The dissertation thesis of **Antonia Diukendjieva-Todorova** is 144 pages long, submitted in English, and comprises an Introduction, three chapters, formulated contributions, a Declaration for the results' originality, a Bibliography of 202 literature sources and a list of 6 publications on the thesis and 8 participations in international and national scientific conferences. The thesis has been illustrated by 16 tables and 25 figures, and it contains two additional Appendices (1 and 2), whose length is 25 pages. In the provided form, the dissertation thesis corresponds to the specific requirements defined in Art. 27(2) from the Council of Ministers' Regulations for the Implementation of the Academic Staff Development Act in the Republic of Bulgaria (ASDARB).

The aim of the dissertation thesis is to evaluate the ADME/Tox properties and to research and clarify the mechanisms of action, related to potential pharmacological effects of the flavonolignans from *Silybum marianum*.

In order to accomplish the **aim** of the dissertation thesis, the following particular **tasks and subtasks** have been outlined:

1. Research of the ADME/Tox properties of flavonolignans from *Silybum marianum*.
 - 1.1. *In vitro* and *in silico* evaluation of the gastrointestinal absorption.
 - 1.2. *In silico* prediction of toxicity and metabolism.
 - 1.3. Molecular modelling of interactions with the human estrogen receptor alpha (ER α).
2. Studies of molecular interactions of flavonolignans from *Silybum marianum* with novel target proteins.
 - 2.1. Evaluation of similarity between selected flavonolignans and drug molecules with known mechanism of action.
 - 2.2. Selection of potential common target proteins for the studied flavonolignans and drug molecules.
 - 2.3. Molecular modelling of flavonolignans' interactions with selected target proteins.
 - 2.4. *In vitro* studies of the flavonolignans' effects on mechanisms involving the selected target proteins.

The timeliness of the dissertation thesis stems from the fact that since ancient times natural products have been used for a plethora of medical purposes, and to this day they still serve as a source of inspiration for the contemporary drug design due to their vast diversity of chemical structures and biological activities. The thesis' topicality is further supported by the instrumentation set for solving the tasks, namely the most advanced, incl. integrated approaches from the field of computer-aided drug design.

The presented list of publications on the topic of the dissertation thesis by **Antonia Diukendjieva-Todorova** includes 6 publications – 4 of which in scientific journals, and 2 conference communications in full text in conference proceedings, all of them written in co-authorship. Four of the publications are referred in globally renowned databases, where 3 of them are published in Impact Factor journals with Q1 and Q2 quartiles, and one is in a journal with an SJR, again in Q2 quartile. The total impact factor of **Antonia Diukendjieva-Todorova's** papers is 11.39. The PhD student is the first authors in all of these publications, which unequivocally demonstrates her contribution to the achieved and presented research results. The presented Reference for 31 citations in Web of Science / 37 citations in Scopus, is yet another undeniable and independent testimonial for the timeliness of the thesis under discussion and the results achieved therein.

The presented synopsis of the dissertation thesis is 58 pages long in its Bulgarian version and 56 pages long in English. It fully covers the essence and contents of the dissertation thesis, including the aim and the tasks set, as well as their execution and the achieved results.

Regarding the thesis itself, I would like to share some views of mine that refer to its organisation. In Chapter 1, Section 3, there are quite a number of details that would have been better exposed in Chapter 2. On the other hand, I consider that the data presented in Chapter 2, Section 2, could have been presented in the respective subsections of Section 1 of Chapter 2, namely, the data from 2.1 could have been given at the end of 1.1, the data from 2.2 – in 1.2, and those from 2.3 – in 1.5.

In support of this proposal, I would note on the one hand the titles of the above listed subsections being identical, and on the other hand, the brevity of subsections 2.1 to 2.3. Sections 1 and 2.3 from Chapter 3 are presented as a generalization of the results presented in the subsections therein, that is, 1.1 to 1.3 and 2.3.1 to 2.3.4, and in this form they fit much better for conclusion.

I should immediately point out that this opinion of mine has the force of recommendation, and it solely refers the manner of thesis organisation, which in no way diminishes the achieved and appropriately presented results pursuant to the accomplishment of the aims and tasks of the thesis.

On the basis of the research elaborated in the dissertation thesis, **Antonia Diukendjieva-Todorova** articulated two main contributions, the second of which comprises 3 subcontributions. I endorse these contributions in the form the PhD student has formulated them.

I personally know **Antonia Diukendjieva-Todorova** since her enrolment in the QSAR and Molecular Modelling Department of IBPhBME – BAS, and I know her as an extremely conscious and responsible team member. Getting familiar with her dissertation thesis reinforced my impression that she is an already established and highly prospective young researcher. I sincerely hope that her potential, as demonstrated in the herewith presented high quality dissertation thesis, as well as her self-demanding and industrious mind-set will allow her a fast track in the academic career.

In forming the overall assessment of the dissertation thesis, one should render account of the requirements formulated in the ASDARB and the IBPhBME's Regulations for its implementation. PhD student **Antonia Diukendjieva-Todorova** not only covers but certainly exceeds the requirements for acquisition of the educational and scientific degree "Doctor of Philosophy", as indicated in the Regulations of IBPhBME for implementation of the ASDARB.

With respect to all of the above, I certify that **the requirements for awarding the educational and scientific degree "Doctor of Philosophy" (PhD) set in the ASDARB and in the Regulations of IBPhBME-BAS for Implementation of the Act have been fulfilled**. After getting familiar with the presented dissertation thesis and the publications it is based on, which give visibility of the results achieved, and after analysis of the significance of these publications and the scientific and applied science results contained therein, I justifiably give my **positive evaluation** and recommend the respected members of the Scientific Jury to vote for awarding **Antonia Georgieva Diukendjieva-Todorova** with the **educational and scientific degree "Doctor of Philosophy"** in Professional Field **4.3. Biological Sciences**, Doctoral Programme **Application of the Principles and Methods of Cybernetics to the field of structure – activity relationships of biologically active substances**.

22 November 2023
Sofia

Signature:



(Prof. Tania Pencheva, PhD)