# REVIEW

**BY PROF. MILKA MILCHEVA MILEVA, PhD**

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**REGARDING:** competition for the academic position "Associate Professor" by field of higher education 7. Health care and sports, professional direction 7.1 Medicine from ZRASRB, announced in the State Gazette no. 28 of 04/02/2024 for the needs of the Biotechnology Department, Metabolomics Laboratory IMicB - BAS

This review was prepared in accordance with Order No. I - 57/23.04.2024 of the Director of the Institute of Microbiology "Stefan Angelov" - BAS (IMicB) by decision of the Scientific Council of IMicB, protocol No. 2 of 03.26.2024. , according to which I am included in the scientific jury of a competition announced in the State Gazette no. 28 of 04/02/2024

**CANDIDATE:** Ch. Assistant Professor Lilia Vladimirova Mihailova, Ph.D. the only candidate

The review of the documents shows that the procedure for disclosure and announcement of the competition has been followed. The presented set of materials complies with the requirements of Chapter IV, Section IV. Terms and conditions for occupying the academic position "associate professor" from the Regulations for the terms and conditions for acquiring scientific degrees and holding academic positions at the "Stefan Angelov" Institute of Microbiology at the Bulgarian Academy of Sciences and includes all necessary documents.

I vaguely know the candidate for the competition; I have no scientific publications in common with her, and I have no conflict of interest, according to the law.

## BRIEF BIOGRAPHICAL DATA

Lilia Vladimirova Mihailova (Vasileva) was born on June 20, 1988, in the city of Plovdiv. In 2013, he graduated from the Medical University of Plovdiv, Faculty of Pharmacy, Plovdiv and obtained a master's degree in Pharmacy. Even as a student, she participated in a student exchange within the framework of the ERASMUS program in Nijmegen (Netherlands).

In the period 2013 - 2016, he specialized in "Analysis of medicinal products" under the supervision of Prof. Danka Obreshkova.

In 2017, she defended a dissertation on a topic at the Department of Pharmacology and Clinical Pharmacology at the Faculty of Medicine of the Medical University - Plovdiv under the supervision of Prof. Dr. Damyanka Getova-Spasova.

In the period 2016 - 2018, he worked as an assistant in the Department of Pharmacology and Medicinal Toxicology at the Faculty of Pharmacy of the Medical University - Plovdiv. In

2018, he won a competition for a researcher - postdoctoral fellow at the Center for Plant System Biology and Biotechnology, Plovdiv. From 2021 until now, he is the chief assistant in the Biotechnology Department, Metabolomics Laboratory at the Institute of Microbiology, Bulgarian Academy of Sciences - Plovdiv.

**EVALUATION OF SUBMITTED MATERIALS IN THE COMPETITION**

In the current competition, Dr. Mihailova presents a list of 37 scientific papers published after obtaining the scientific and educational degree "Doctor".

The presented publications are distributed by groups of indicators in accordance with the requirements of the RSARB in the relevant professional field, as follows: 25 publications and reports published in scientific publications, referenced and indexed in world-renowned databases with scientific information, of which 12 by indicator B and 12 by indicator D. The table under indicator D also includes 13 publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes.

The scientific topic that the candidate develops is in the field of molecular pharmacology, pharmaceutical biotechnology and biological activity of natural products. Her interests are focused on socially significant diseases and modern approaches to their prevention and pharmacotherapy. Dr. Mihailova and her team are the only ones working in our country with preclinical models of obesity in vitro in human adipocytes and *in vivo* in nematodes of the species *Caenorhabditis elegans*. With her expertise, she actively participates in the preparation of project proposals, planning and conducting experiments on the various scientific topics developed in the Metabolomics laboratory.

The publication activity of Dr. Mihailova fully meets the requirements for the growth of the academic staff. It is also worth noting the fact that the candidate has publications in Q1 positioned international journals with high impact such as Food Frontiers, Phytochemistry Reviews, Biomedicine & Pharmacotherapy, International Journal of Molecular Sciences, etc.

**MAIN SCIENTIFIC CONTRIBUTIONS**

Dr. Lilia V. Mihailova's scientific contributions are in the field of molecular pharmacology of obesity, longevity and skin aging with a focus on the mechanisms of action of natural substances of plant origin.

The enormous scale that obesity has acquired in recent decades, as well as the unfavorable forecasts for the development of this global problem, determine the relevance and practical importance of the scientific topics that Dr. Mihailova develops. In her work, she looks for alternatives to solve this problem. The research is multi-layered, combinative, with modern analytical approaches aimed at identifying plant secondary metabolites with activity against obesity and premature aging, as well as determining their molecular mechanism of action. In addition, Dr. Mihailova evaluates the possibility of potential synergistic interactions when incorporating natural molecules into hybrid combinations with established drugs.

**The main contributions of the research Ch. Assistant Professor Lilia V. Mihailova, Ph.D., are in the following areas:**

- Adaptation of preclinical models of obesity in vitro in human adipocytes and *in vivo* in *Caenorhabditis elegans*;
- Anti-obesogenic potential and mechanism of action of plant extracts and pure substances;
- Enriching the basic knowledge about the role of inhibition of phosphoinositide-3-kinase (PI3K) / protein kinase B (AKT), as the main one in the complex molecular signaling pathways affected in obesity;
- Evaluation of extracts and pure substances to influence the molecular mechanisms of longevity in *C. elegans*;
- Adaptation of preclinical models of psoriasis and UV-induced skin aging in vitro in human keratinocytes;
- Evaluation of immunoregulatory activity and potential for application in chronic stress of extracts and pure substances from adaptogenic plants;

In her research work, the candidate applies a wide range and skilful combination of conventional and classical with modern experimental approaches to develop new experimental model systems in the conduct of preclinical studies. A screening platform for anti-adipogenic potential of plant extracts and natural molecules in an *in vitro* model of adipocyte differentiation of human fat cells was developed. A model system was introduced and optimized for the evaluation of anti-obesogenic potential at the organismal level in nematodes of the species *Caenorhabditis elegans*. These model systems provide opportunities to evaluate the potential of a large number of (natural) substances and to analyze in depth the complex network of molecular signaling pathways that are disrupted in obesity.

Screening for anti-adipogenic effect of a wide panel of medicinal plant extracts in human adipocytes was performed. Those showing the most pronounced activity were subjected to metabolic profiling based on nuclear magnetic resonance (NMR) spectroscopy and high-performance liquid chromatography. A mechanism of action for *Ononis spinosa* L. extract and the pure substances ononin and maakiain in an obesity model on human adipocytes is proposed. When treated with rosmarinic acid, anti-adipogenic and anti-inflammatory activity was found, mediated by suppression of lipogenesis, activation of lipolysis, reduction in the levels of key transcription factors (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα).

A mechanism of action is proposed for an extract of *Alchemilla monticola* Opiz. and its secondary metabolites astragalin and quercitrin in a human adipocyte model of obesity. *A. monticola* (*A. monticola*) extract markedly suppresses the phosphoinositide-3-kinase (PI3K)/protein kinase B signaling pathway in human adipocytes. This activity was not observed when the pure substances astragalin and quercitrin were administered alone. Betulinic acid, characteristic of jujube extract, was found to exert an anti-adipogenic effect on this signaling pathway in an in vitro model of human adipocyte obesity and, respectively, regulate insulin-mediated lipid accumulation in *C. elegans* subjected to a high-glucose diet. The anti-inflammatory potential was determined and a mechanism of action of extracts from biotechnologically obtained plant cultures of *Lavandula angustifolia* L. and *Harpagophytum procumbens* (Burch.) DC ex Meisn was proposed and isolated pure substances rosmarinic acid and leukoseptoside A in an in vitro model of psoriasis induced by a combination of inflammatory cytokines. A standardized extract of goldenrod (*Rhodiola rosea* L.) beneficially affects learning and memory in both healthy and rats subjected to scopolamine-induced amnesia and a chronic stress model. Salidroside and curcumin have been shown to exhibit immunomodulatory, anti-inflammatory and anti-depressive effects in rats. The combination of

the two substances is a promising therapeutic approach for the treatment of chronic stress and mild to moderate depression.

The publications submitted for participation in the competition for an associate professor are in the field of the announced competition, namely the field of higher education 7. Health and sports, professional direction 7.1 Medicine. In the reference to the research work of Ch. Assistant Professor Lilia V. Mihailova, Ph.D., 6 contributions have been noted, the wording of which I fully agree with. **DIRECTIONS FOR HER FUTURE WORK** are also duly described. They are a natural extension of the research work carried out so far and the prospects are their deepening. The specific plans can be broadly outlined as follows:

- Pharmacology and biochemometrics - the main areas of scientific interest include evaluating the pharmacological potential of extracts and pure molecules in model systems of human adipocytes, keratinocytes, fibroblasts and Caenorhabditis elegans; correlations of metabolic profiles with antiobesity activity, mitochondrial damage, and UV-induced skin aging; and potential to extend lifespan and reduce age-related metabolic disorders.

- Metabolomics and metabolic profiling – combining the various metabolomics platforms such as NMR, HPLC combined with mass spectrometry in order to more fully elucidate the changes in the metabolome of both plant extracts and model organisms under different conditions – physiological, aging, stress and experimental treatment; using functional metabolomic analysis methods such as assessment of changes in lipid metabolism.

- Scientific and applied research in the field of pharmaceutical biotechnology - biosynthesis, isolation and purification of economically important plant metabolites;

- Development of biotechnological processes for creating new products for cosmetics (on the basis of endemic and endangered plant species and their *in vitro* systems) and against obesity and related metabolic disorders.

**REFLECTION OF THE CANDIDATE'S SCIENTIFIC PUBLICATIONS IN BULGARIAN AND FOREIGN LITERATURE**

In the current competition, Dr. Mihailova participated with 37 publications with a total impact factor of 130.96, of which 19 were published in Q1 journals for the relevant scientific field, in 13 of them she was the lead or corresponding author. The candidate's scientific output has been published in renowned scientific journals, which fully explains the number of received citations – over 400 citations in Scopus, excluding self-citations. The Hirsch index is 12.

For the competition, the candidate has presented over 30 participations at international scientific forums, 8 participations in national and international projects. He is the head of 1 national project and coordinates the scientific team from IMicB on the PlantaSYST project.

In 2020, he received the "Young Phytochemist" Award from the Bulgarian Phytochemical Association for achievements in preclinical research related to revealing the potential of natural compounds as anti-obesity agents.

In 2023, Dr. Lilia V. Mihailova is among the three nominees for the "Pythagoras" award for the best young scientist in the field of Life Sciences and Medicine. She is a member of the team that received the IMicB Annual Award for Scientific Excellence in early 2024.

**GENERAL ASSESSMENT OF THE CANDIDATE'S COMPLIANCE WITH THE MANDATORY REQUIREMENTS OF ZRASRB**

According to the submitted report on the implementation of the minimum requirements of the RSARB and those of the IMicB - BAS, Ch. Assistant Professor Lilia Vladimirova Mihailova, Ph.D., exceeds the national and specific requirements for occupying the academic position "Associate Professor", as follows:

**According to indicator A - 50** points with a defended PhD thesis;

**According to indicator B** - 12 articles are presented in quartile Q1, with a total impact factor of 87.66, and the sum of the points is **134.17** out of the required **100**;

**According to indicator G** - Dr. Mihailova presented 12 articles published in Q1 quartile journals; 2 in quartile Q2; 1 in quartile Q3 and 1 in quartile Q4, with a total impact factor of 43.30. The sum of the points is **264.36,** with a required **200**;

**According to indicator D - 6525** points out of the required **50**;

**According to indicator E - 156.90** points, as for AD "Associate professor" no points are required for this indicator.
Total points are **7130.43** out of **400** required.

**CRITICAL NOTES –** some minor technical inaccuracies are noticeable, which I do not find essential.

**IN CONCLUSION**

The analysis of the research activity of Ch. Assistant Professor Lilia Vladimirova Mihaylova, Ph.D., shows that she is completely in the field of the announced competition. The obtained results are original, up-to-date and of public importance. The contributions have a targeted fundamental character, with a clearly defined practical orientation - they reveal opportunities and perspectives for new research on an extremely topical global problem - obesity.

The scientific research activity of the candidate exceeds several times the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), the Regulations for the Implementation of the ZRASRB, the Regulations of the BAS, as well as the Institute of Microbiology "Stefan Angelov" - BAS. The presented materials and results fully correspond to the specific requirements adopted in connection with the Regulations of the Institute of Microbiology "Stefan Angelov" - BAS. In view of everything stated above, I believe that Ch. Associate Professor Dr. Mihailova is an established researcher with a bright scientific profile.

As a member of the scientific jury for the announced competition, **I give a positive assessment and confidently recommend the members of the honorable jury to vote for the election of Ch. Assistant Professor Lilia Vladimirova Mihaylova, Ph.D., to the academic position of Associate Professor in professional field 7.1 Medicine for the needs of the Department of Biotechnology, Metabolomics Laboratory of Instistute of Microbiology - Bulgarian Academy of Sciences.**

08/05/2024 Prepared the review: **На основание чл. 2 от ЗЗЛД**

Sofia / Prof. Dr. Milka Mileva /