

REVIEW

Presented by prof. Lyudmila Vladimirova Kabaivanova-Milanova, “Stephan Angeloff” Institute of Microbiology (SAIM) – BAS, elected as a member of the Scientific Jury and reviewer based on order № 1-52/28-04-2023 of the Director of SAIM prof. Penka Petrova, DSc, following the proposal of the Scientific Council of the Institute, on the materials, regarding the competition for the academic position "Professor" in the field of higher education 7. Healthcare and sports, professional direction 7.3. Pharmacy.

Candidate: Assoc. Prof. Milka Milcheva Mileva, PhD

Common part

The competition for the occupation of the academic position "professor" in the field of higher education 7. Health care and sports, professional direction 7.3. Pharmacy is for the needs of the "Virology" Department, Laboratory "Biological Response Modifiers and Pathogenesis of Viral Infections" of IMSA and was promulgated in the "State Gazette", (State Gazette, No. 21 of 07.03.2023). The only candidate is Assoc. Prof. Milka Milcheva Mileva, PhD from the same institute. The review of the documents shows that the procedure for disclosure and announcement of the competition has been followed. The presented set of materials has also been prepared in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB) and the Regulations for its application, as well as the Regulations of the BAS and IMSA.

Brief biographical data

Assoc. prof. Milka Mileva received her Master's degree at the Chemistry Faculty of Plovdiv University "St. Paisii Hilendarski" as "Master of Chemistry". The candidate received her PhD degree in 2002 in the Department of Medical Physics and Biophysics, MF of the Medical University - Sofia with the thesis topic: "Influence of rimantadine, vitamin E and cold immobilization stress on oxidative damage in an experimental model of influenza virus

infection". After successfully defending her dissertation, she held the position of "Assist. prof." at the "Stephan Angeloff" Institute of Microbiology - BAS, Section "Microbial Biochemistry". Later in 2011 she won a competition and was appointed as an "Associate professor" in the Department of "Virology" at the same institute, a position she holds to this day.

General presentation of scientific works

Associate Professor Mileva participates in the competition with a **total of 41** publications. Of these, **20** are in issues that are referenced and indexed in world-renowned scientific information databases and **21** are published in other scientific journals. The interdisciplinary profile of her research is noticeable.

Her works participating in the competition were cited **66** times, and for the entire scientific internship there were **a total of 716 citations**, with an **h-index of 15**. Of all published scientific works, the **impact factor** of Prof. Mileva reached **80.851**. Results of her research work have been presented at more than **70** national and international scientific forums.

According to the submitted report on the fulfillment of the minimum requirements for the academic position "professor" (NATIONAL CRITERIA UNDER ZRASRB for the relevant professional field), it can be seen that the candidate meets all the requirements - she submitted materials correspond to **1567.63 points** out of the required **750**. In the groups of indicators **A – 50 points; B – 111.78 points; G – 262.85; D – 870; E – 273**.

With regard to the reference for the fulfillment of the ADDITIONAL CRITERIA for AD "professor" at IMSA, the candidate has **20 publications after "associate professor"**, in refereed journals, in **17** of which she is the lead (first and/or corresponding) author and one university textbook.

The scientific activity of Assoc. prof. Mileva can be highly evaluated, based on her high scientometric indicators.

Project and teaching activity

The project activity and teaching activity of Associate Professor Milka Mileva is active. She took part in the implementation of **13 scientific research projects**, **5** of which she is the **head** of. Prof. Mileva's contribution to the project activity is a strong point in her scientific biography.

The educational and teaching activities of the candidate include 800 hours of lectures and 240 hours of exercises in master's and other educational programs at Sofia University, Medical University, Southwest University, as well as 120 hours of lectures and 190 hours of exercises at "Yordanka Filaretova" Medical College for the period 2005 – 2009. She leaded **2 doctoral students** who have **defended their theses**, **1** has been awarded **with the right to defend** it and another 1 is in the ongoing procedure.

Expert and administrative activity

Milka Mileva is a member of 2 editorial boards and is an anonymous reviewer of more than 40 publications abroad, participates in Scientific Juries and Examination Committees in procedures. Along with the scientific activity, the administrative one cannot remain aside. Since 2017 Assoc. prof. Mileva became the head of the laboratory "Modifiers of the biological response and pathogenesis of viral infections" in the department of "Virology" and the chairman of the General Assembly of scientists at IMSA. She is also a member of the Scientific Council of the same institute.

Scientific contributions

The main contributions of Assoc. prof. Mileva's research activities are in the following fields:

❖ Oxidative damage and the role of antioxidants in the prevention and therapy of diseases associated with the development of oxidative stress in experimental models *in vivo*.

- Oxidative damage in influenza virus infection and optimization of therapeutic approaches, including a combination of specific inhibitors of viral replication and non-specific adjuvants to control virus-induced pathogenesis in target organs;
- Markers of oxidative stress and antioxidant protection in conditions of antioxidant deficiency - non-alcoholic fatty liver disease and acute radiation syndrome;
- Newly synthesized hydrazide-hydrazone derivatives of isoniazid as suitable antituberculosis drug candidates with low toxicity and good bioavailability;
- Role of endogenous cannabinoids in stress response modulation.

❖ Pharmacological potential of plant extracts, technological products obtained by hydro-steam distillation of essential oils from Bulgarian oil-bearing roses and their ingredients in experimental models *in vivo* and *in vitro*.

- Chromatographic profile of the essential oils, hydrosols and wastewater obtained during the water-steam distillation of the Bulgarian oil-bearing roses *Rosa damascena* Mill., *Rosa alba* L., *Rosa centifolia* L. and *Rosa gallica* L.;
- "High value products" in industrial waste - study of the antineoplastic activity and redox-modulating capacity, antiviral, antibacterial, anti-cytotoxic and antigenotoxic effect of wastewater obtained during the water-steam distillation of Bulgarian oil-bearing roses;
- Redox-modulating capacity and biological potentials of extracts from Bulgarian plants and microalgae, rich in polyphenols - antioxidant, anti-coronavirus effectiveness, suppression of intracellular oncogenic superoxide and antibacterial activity.

The studies and conducted experimental work are aimed at developing and optimizing new therapeutic approaches and strategies for the prevention and therapy of virus-induced diseases, studying and controlling oxidative damage and virus-induced pathogenesis in target organs during influenza virus infection. Redox processes are studied in depth, which are a

key mechanism in maintaining cellular homeostasis and the normal functioning of the body. Disturbances in this mechanism also play a decisive role in the pathogenesis of malignant, neurodegenerative, atherogenic, autoimmune diseases, diabetes, etc., the common feature of which is the development of oxidative stress due to a disruption of the redox balance in cells, tissues and body fluids. Alternatives are being sought to address one of the major problems with specific influenza chemotherapy, which is the rapid development of resistance. A therapeutic approach involving comedication of the glutathione precursor S-adenosyl-L-methionine (SAM) and the specific inhibitor of viral replication oseltamivir was investigated and very good protection was found on the virological parameters - viral titer, protection index, mortality and mean time of survival, as well as on biochemical markers of oxidative stress in target organs.

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 for conducting studies such as the chromatographic profile of essential oils, hydrosols and wastewaters obtained during hydro-steam distillation of Bulgarian oil-bearing roses to study the antineoplastic activity and redox-modulating capacity, antiviral, antibacterial, anti-cytotoxic and antigenotoxic effect of these wastewaters.

The themes developed by Milka Mileva are undeniably relevant, as the correct actions for the prevention and treatment of socially significant diseases would lead to an extension of life expectancy and improvement of people's quality of life.

The candidate's contributions are related to biomedicine and ecology, which shows a clear direct connection between the results of Dr. Mileva's research activity and human health and the protection of his living environment.

More specifically, her contributions can be defined as follows:

- The pathogenetic picture of infection caused by influenza virus A/Aichi/2/68 (H3N2) has been clarified - increased values of markers of oxidative stress in the liver and liver, as well as in the stomach of infected animals, reduced levels of glutathione and alpha tocopherol and activity of the antioxidant enzymes catalase

and superoxide dismutase, and biochemical changes were found to be in sync with histological findings;

- An approach has been adapted to control the symptoms and physiological damage of influenza infection, including the administration of a specific antiviral agent oseltamivir in combination with SAM as an adjuvant and precursor of the endogenous antioxidant glutathione, with promising results showing the possibility of overcoming viral resistance on the basis at a four-fold lower dose of oseltamivir;
- A platform was created for the study of the phytochemical profile and biological potential of the Bulgarian oil-bearing roses and the wastewater from their production;
- For the first time, a comparative phytochemical analysis was performed in a comparative aspect of the biological activities - anti-herpesvirus, anti-bacterial and anti-tumor of the aromatic products from the Bulgarian *Rosa alba* L. and *Rosa damascena* Mill.
- The pharmacological potential of rose oils in their combination with acyclovir in controlling herpesvirus infection has been established;
- For the first time, a complex of classical cytogenetic methods was applied in three types of experimental test systems - higher plants *in vivo*, ICR mice *in vivo* and human lymphocytes *in vitro* to study the oils, hydrosols and wastewaters from their distillation, which do not exhibit significant cytotoxic and genotoxic effects.

CONCLUSION:

The documents and materials presented by Associate Professor Milka Milcheva Mileva meet all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Application and the Regulations for the Development of the Academic Staff of IMSA and BAS for the acquisition of the academic position "Professor".

The presented materials give me reason to confidently express my positive opinion regarding the submitted application for the academic position "professor".

The obtained results and contributions are original, up-to-date and of public importance. They reveal opportunities and perspectives for new research on current problems, aimed at applying the biological activities of various plants as valuable pharmacological agents in the prevention and therapy of socially significant diseases such as influenza, tuberculosis, herpesvirus infections, as well as the development of new technologies for the processing of wastewater from rose production based on their low toxicological profile.

From everything that has been said so far, it can be seen that this candidate is an established specialist enjoying authority in scientific circles. As a member of the Scientific Jury for the announced competition, I give a positive assessment and recommend to the members of the esteemed Scientific Council of the IMSA at the BAS to elect assoc. p rof. Dr. Milka Milcheva Mileva to the academic position of "Professor" in in the field of higher education 7. Healthcare and sports, professional direction 7.3. Pharmacy.

01.06.2023

/prof. Lyudmila Kabaivanova, PhD/