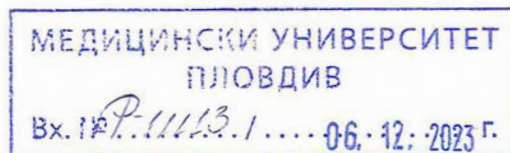


TO
THE CHAIRMAN OF THE SCIENTIFIC JURY,
DETERMINED BY ORDER NO. R-3054/23.10.2023
OF THE RECTOR OF THE MEDICAL UNIVERSITY - PLOVDIV
V. APRILOV BLVD. NO. 15A, 4002
PLOVDIV



On your Protocol No. 1/ dated 26.10.2023

Attached I present:

OPINION

by competition for the academic position of ASSISTANT PROFESSOR

in scientific specialty Pharmacology /incl. pharmacokinetics and chemotherapy/, field of higher education 7. Health care and sports, professional direction 7.1 Medicine at the "Pharmacology, toxicology and pharmacotherapy" department for the teaching of Bulgarian and English - one announced for the needs of MU-Plovdiv. in SG. issue 59/11/07/2023

Drafted opinion: Prof. Dr. Snezha Zlateva Zlateva, d.m.

Research specialties: internal medicine and clinical toxicology

Institution: MU "Professor Dr. Paraskev Stoyanov" - Varna

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Заличено на основание
Чл.5 §1, б."В" Регламент (ЕС)2016/679

OPINION

by Prof. Dr. Snezha Zlateva Zlateva, d.m.

Professor at the Department of "Pharmacology, Toxicology and Pharmacotherapy" of the Faculty of Pharmacy, Medical University - Varna

Regarding: competition for the academic position "Docent", in "Pharmacology (incl. pharmacokinetics and chemotherapy)", field of higher education 7 "Health and sports", professional direction 7.1. "Medicine", to the department of "Pharmacology, toxicology and pharmacotherapy" for the teaching of Bulgarian and English - one, announced in SG no. 59/11.07.2023 for the needs of the Faculty of Pharmacy of MU-Plovdiv.

By order No. P-3054/23.10.2023 of the Rector of MU - Plovdiv, I was elected as a member of the Scientific Jury, and according to Protocol No. 1/26.10.2023 of the first meeting of the Faculty of Science, I was appointed to prepare an opinion on the procedure for occupying the academic position of "associate professor", majoring in "Pharmacology (incl. pharmacokinetics and chemotherapy)".

The only candidate in the competition is a mag. Pharm. Vesela Yulieva Kokova, d.m. The competition procedure has been followed and the applicant's documents are in accordance with 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 at the Medical University - Plovdiv and the criteria for filling the academic position laid down therein "docent" position.

I. Analysis of the candidate's career profile:

Vesela Kokova was born in 1987. She graduated from the "Yvan Vazov" language high school in the city of Plovdiv in 2006 with excellent results. She graduated as a master pharmacist at the Faculty of Pharmacy of the MU Plovdiv in 2012 with excellent results, for which she was awarded a certificate from the Bulgarian Pharmaceutical Union.

In 2017, he acquired the specialty "Clinical Pharmacy", and in 2021, the second specialty "Pharmacology and Pharmacotherapy". In 2017, he developed a dissertation and received the educational and scientific degree "Doctor" in the specialty "Pharmacology". Participated in mobilities under the Erasmus program in Spain, Hungary and Slovakia. He speaks Spanish, Russian and English.

In 2012, she was elected as an assistant, and in 2017, as a chief assistant in the Department of "Pharmacology and Medicinal Toxicology" at the Faculty of Pharmacy at the Medical University - Plovdiv, being the deputy head of academic work and the deputy head of

monitoring resources and measurement to the Department of Pharmacology, Toxicology and Pharmacotherapy.

The general work experience and the teaching experience of the assistant Vesela Kokova is 11 years old. Actively participates in theoretical and practical training in pharmacology for students of medicine, dentistry and pharmacy, and in toxicology and pharmacotherapy for students in pharmacy. Takes part in semester exam sessions "Erasmus" program, in projects of Medical University - Plovdiv. He presents the results of his scientific activity in our and foreign scientific publications, publishes a monograph. It also takes part in publishing textbooks and study aids for students. The teaching activity of the candidate brings a total of 1284.17 points under indicator group G.

II. General description of the submitted materials for the competition.

Mag. Pharm. Vesela Kokova, d.m., submits in this competition the necessary documents, corresponding to the ZRASRB and the Regulations for the development of the academic staff at the Medical University - Plovdiv, which are: application for admission to participation in the competition, curriculum vitae, diplomas for completed higher education and for acquired "Doctor", certificate of internship in the specialty, academic reference for a study load of 627 to 1152 hours per year from 2019 to 2023, attestation sheet with a rating of "very good" from 2018 to 2020, abstract of dissertation work "Experimental study of the pharmacological effects of etifoxine on nerve and neurovascular structures", habilitation work - monograph "Therapeutic potential of alginate and ficoidan", list of publications and citations in refereed and non-refereed journals, diplomas for recognized specialties - "Clinical Pharmacy" and "Pharmacology and Pharmacotherapy", documents for co-authorship in textbooks and teaching aids, participation in national and international projects, references for original scientific contributions and for self-assessment for fulfilling the specific scientometric requirements of MU Plovdiv, copies and summaries of the publications in Bulgarian and English, declaration of originality and authenticity of the attached documents, academic references related to educational, research and administrative activities, training of pharmacy trainees, NACID card, documents for English language proficiency, list of participations in international and national forums and conferences.

III. Evaluation of the scientific works of the candidate for the overall academic development.

III.1. General Characteristics of scientific production and publication activity;

Mag. Pharm. Vesela Kokova presents 41 full-text scientific publications, of which 17 are in refereed scientific publications in the Scopus and Web of Science databases and 23 are in non-refereed journals and collections. 15 of the published articles are in journals with an impact factor. 25 of the published articles are in English. The impact factor of published full-text articles is 34.925. The candidate also contributed 12 reports and abstracts, 3 of which were in journals with an impact factor. The impact factor of reports and abstracts is 12.075.

III.2. Scientific activity - dissemination and application of the scientific and practical achievements of the candidate/s among the scientific community;

Mag. Pharm. V. Kokova is the first author in the published full-text scientific publications (22); second author (11) and last author (6). The total number of points from the actually published articles is 639.65 for indicator group D. The candidate participates in the author team of 2 university textbooks and 13 university textbooks - collections of tests and prescription tasks in pharmacology, toxicology and biophysics. They are the basis of the training of students in medicine, pharmacy, dentistry, assistant pharmacists, nurses and midwives, medical laboratory technician, X-ray laboratory technician and rehabilitator.

III.3. Participation in implementation and management of projects;

Mag. Pharm. V. Kokova participated in 10 national and 7 international scientific or educational projects.

III.4. Scientific and creative achievements (scientific authority);

V. Kokova presents her scientific work in many national and international forums, which build her authority as a scientist - a total of 41 scientific forums, of which 17 are international and 24 national scientific forums. The presented scientific reports treat current scientific and applied problems and make a significant contribution to the announced competition for associate professor in "Pharmacology (incl. pharmacokinetics and chemotherapy)".

IV. Evaluation of the monographic work or equivalent publications submitted by the candidate for participation in the "ASSISTANT PROFESSOR" competition.

IV.1. Evaluation of the monographic work

The monograph "Therapeutic potential of alginate and fucoidan" examines the possibility of creating medicinal products of natural origin. Polysaccharides in the

composition of algae exhibit a wide range of biological activities and have the potential of new agents for treatment and/or prevention. The monograph includes 4 chapters: 1. Algae as food, fodder and for medicinal purposes; 2. The polysaccharides contained in the algae and the biological effects established so far; 3. Alginates and their biological effects - antitumor, anti-inflammatory, neuroprotective, immunomodulatory, antioxidant, antibacterial and antimycotic, prebiotic, antidyslipidemic, antihypertensive, hypoglycemic effects, positive effect on obesity and stimulation of cell proliferation, in addition - their ability to extract some heavy metals from the body, protective effect on the gastric mucosa, cardioprotective and antiviral effects; 4. Fucoïdan, pharmacokinetics and biological effects (anti-inflammatory, immunomodulatory, antitumor, antioxidant, antithrombotic, antifungal, antibacterial, antiallergic, metabolic, prebiotic effects, effects on angiogenesis and additional - effect on bone remodeling, ability to extract lead from the body, stimulation of hematopoiesis, neuroprotective, antiparasitic). The bibliography includes 377 literary sources. The monograph has modern scientific and applied merits and is an original contribution in the field of the announced competition for associate professor of pharmacology. It will be of benefit to scientists working in the field of experimental pharmacology and a starting point for the creation of new medicinal products based on algae.

IV.2. Evaluation of the publications submitted for participation in the competition for "ASSISTANT PROFESSOR"

In scientific production, the most important areas of scientific interest on the part of the candidate are:

1. Pharmacological studies of substances of natural origin and homeopathic products

1. Isolation, structural characterization and study of anti-inflammatory and antioxidant effect of fucoidan extracted from brown algae of the species *Cystoseira crinita* (Duby) Borry (Ericaria crinita (Duby) Molinari & Guiry), distributed in the Black Sea (publications 13.1.14. ; 13.1.17.; 14.1.15.; monograph).

2. Isolation, structural characterization and study of anti-inflammatory effect of alginate extracted from brown algae of the species *Cystoseira crinita* (Duby) Borry (Ericaria crinita (Duby) Molinari & Guiry) distributed in the Black Sea (publications 13.1.15.; monograph).

3. Study of antibacterial and anti-inflammatory effect of Bulgarian propolis (publications 13.1.7.; 14.1.1.).

4. Immunomodulatory effect, influencing the blood picture and the levels of CD34+ hematopoietic stem cells from substances of natural origin and biocompatible products (publications 13.1.3; 14.1.9.; 14.1.10; 14.1.13; 14.2.2.; 14.2.4.)

5. Determination of acute toxicity of *Tanacetum vulgare* (publication 14.1.16).

II. Pharmacological study of anxiolytic and antiepileptic drugs

1. Experimental in vivo and in vitro studies of etifoxine, in connection with the dissertation work (publications 13.1.5.; 13.1.11.; 13.1.16.; 14.1.5.; 14.2.5.; 14.2.7.) .

2. Pharmacological study of pregabalin (Publications 13.2.1.; 13.2.2.; 13.2.3.; 13.3.1.; 14.1.8.; 14.2.3.).

3. Experimental in vivo and in vitro studies of retigabine (Publications 13.1.2.; 13.1.4.; 13.3.2.; 14.1.4.; 14.1.11.; 14.1.12.; 14.1.14.)

III. A study of substances that activate bitter taste receptors (TAS2Rs)

1. Pharmacological study of TAS2Rs agonist - denatonium benzoate (publications 13.1.12; 13.1.13)

IV. Study of the influence of the dosage form on the pharmacological and organoleptic properties of substances of natural and synthetic origin.

1. Masking of the bitter taste of enalapril maleate by precipitation and spray drying methods (Publications 13.1.8.; 13.1.9.; 14.2.6.).

2. Investigation of antihyperalgesic effect of aqueous leaf extract include in two semi-solid dosage forms (publications 13.1.6.).

Scientific contributions of the candidate

In the scientific developments of mag. Pharm. Veselin Kikova has scientific-theoretical and applied-practical contributions.

Contributions with scientific and theoretical application:

1. The chemical composition and structure of fucoidan extracted from the brown algae *Cystoseira crinita* (Desf.) Borry (*Ericaria crinita* (Duby) Molinari & Guiry) distributed in the Black Sea have been identified for the first time.
2. For the first time, the anti-inflammatory effect of a single dose of fucoidan from *C. crinita* was investigated in a histamine-induced and carrageenan-induced paw edema model in rats.
3. For the first time, the serum levels of the pro-inflammatory cytokines IL-1 β , TNF- α and IL-6 and the serum concentration of the anti-inflammatory cytokine IL-10 were investigated after single and repeated (14-day) administration of *C. crinita* fucoidan in a model of lipopolysaccharide-induced systemic inflammation in rats.
4. For the first time, the level of the pro-inflammatory cytokine TNF- α in peritoneal fluid was investigated after a single administration of fucoidan from *C. crinita* in a carrageenan-induced peritonitis model in rats.
5. For the first time, the antioxidant activity of fucoidan from *C. crinita* (*Ericaria crinita*) was investigated by means of two tests: DPPH test and FRAP.
6. For the first time, the chemical composition and structure of alginate extracted from brown algae of the species *Cystoseira crinita* (Desf.) Borry (*Ericaria crinita* (Duby) Molinari & Guiry), harvested from the Bulgarian Black Sea, was identified by means of infrared spectroscopy (FTIR), size exclusion chromatography equipped with multi-angle laser light scattering (SEC-MALS) and nuclear magnetic resonance (¹H NMR).
7. For the first time, the anti-inflammatory effect of a single dose of *C. crinita* alginate was investigated in a histamine-induced and carrageenan-induced paw edema model in rats.
8. For the first time, the serum levels of the pro-inflammatory cytokines IL-1 β , TNF- α and IL-6 and the serum concentration of the anti-inflammatory cytokine IL-10 were investigated after single and repeated (14-day) administration of *C. crinita* alginate in a model of lipopolysaccharide-induced systemic inflammation in rats.
9. For the first time, the level of the pro-inflammatory cytokine TNF- α in peritoneal fluid was investigated after a single administration of *C. crinita* alginate in a rat model of carrageenan-induced peritonitis.
10. For the first time, the effect of the application of Bulgarian propolis on aerobic and anaerobic microflora in adolescents with plaque-induced gingivitis was evaluated.

11. For the first time, the influence of a total extract of the leaves of *Haberlea rhodopensis*, Bulgarian propolis, *Arnica montana* 9 CH and *Ledum palustre* 9 CH on the levels of CD34+ cells in the blood of rodents was investigated.
12. A new and promising experimental model of neuromuscular connection is presented in studying the mechanism of action of etifoxine on neuromuscular transmission in skeletal muscle.
13. The lack of effect of etifoxine on N-acetylcholine receptors and Cav1.2 and Cav1.3 channels is scientifically substantiated and experimentally confirmed.
14. The influence of etifoxine on learning and memory processes in intact rats was studied.
15. In an experimental model of diazepam-induced amnesia, a neuroprotective effect of etifoxine was recorded.
16. The lack of development of tolerance and withdrawal syndrome to pentylenetetrazole was demonstrated after 14 days of oral administration of pregabalin in rats.
17. For the first time in the available literature, the "hangman" test was used to evaluate the locomotor activity of rats treated with pregabalin.
18. It has been shown that 14 days of oral administration of retigabine does not lead to the development of tolerance in terms of the antiepileptic effect to pentylenetetrazole in rats, as well as the absence of a withdrawal syndrome when the medication is stopped abruptly.
19. For the first time, the muscle relaxant effect of retigabine is explained by a change in the reactivity of the muscles to acetylcholine.
20. For the first time, the involvement of Kv7.2-5 channels in the established myorelaxant effect of retigabine on smooth muscle was demonstrated.
21. For the first time, the influence of retigabine on learning and memory processes was investigated in intact rats and in rats with a PTZ-kindling model.
22. The results for the antinociceptive effect of retigabine are of a confirmatory nature.
23. For the first time, the anti-inflammatory effect of denatonium benzoate was investigated in a model of histamine-induced and carrageenan-induced paw edema in rats.
24. Antihistaminic activity of denatonium benzoate has been demonstrated for the first time in vitro.
25. For the first time, the carrageenan-induced hyperalgesia model was used to evaluate the antialgesic effect of denatonium benzoate.

26. For the first time, PGE2 levels were monitored in vivo in rats treated with carrageenan and denatonium benzoate.
27. The potential of Eudragit EPO® for taste masking of enalapril maleate by precipitation and spray drying methods was investigated for the first time. The precipitation method results in unsatisfactory taste masking of enalapril maleate due to the presence of a large amount of unbound drug substance.

Contributions with practical application:

1. For the first time, fucoidan was extracted from brown algae of the species *Cystoseira crinita* (Desf.) Borry (*Ericaria crinita* (Duby) Molinari & Guiry) distributed in the Black Sea. Optimized extraction process, in order to obtain higher yield and purity of the polysaccharide.
2. For the first time, the influence of the methods of purification of the starting material on the quantitative yield and the purity of the obtained fucoidan was studied. The purity of fucoidan extracted from *C. crinita* was determined by quantitative analysis of total polyphenols by the method of Singleton and Rossi, as well as the content of proteins by the method of Bradford.
3. For the first time, DPPH radical-trapping antioxidant activity as well as ferric ion reducing ability (FRAP) of fucoidan from brown algae *C. crinita*, distributed in the Black Sea, was established.
4. The proven anti-inflammatory effect of fucoidan from *C. crinita* after single and repeated (14-day) administration can be the basis for the development of a new medicinal product with an anti-inflammatory effect.
5. For the first time, alginate was extracted from brown algae of the species *Cystoseira crinita* (Desf.) Borry (*Ericaria crinita* (Duby) Molinari & Guiry), harvested from the Bulgarian Black Sea.
6. The purity of the alginate obtained from *C. crinita* was proven by determining the content of residual sulfate groups, total polyphenols and protein.
7. The results of anti-inflammatory effect of *C. crinita* alginate may find application for the preparation of a new medicinal product with anti-inflammatory effect.
8. The results of anti-inflammatory and antimicrobial effect of propolis are grounds for its use in addition to established methods for mechanical and

chemical cleaning of dental plaque, with the aim of prevention or achieving a better therapeutic effect.

9. The data on increasing the number of CD34+ hematopoietic stem cells in the blood of rats after administration of an extract of *Haberlea rhodopensis*, Bulgarian propolis, the homeopathic products *Arnica montana* 9 CH and *Ledum palustre* 9 CH are of an original nature, and those of fucoidan – of a confirmatory nature. The experimental results of an increased number of CD34+ cells after administration of *Aphanizomenon flos-aquae* confirm the data obtained in humans.
10. For the first time, an increase in the total number of leukocytes and the number of neutrophil granulocytes in the blood of rats under the influence of the homeopathic products *Arnica montana* 9 CH and *Ledum palustre* 9 CH was found, and the data on an increased number of leukocytes after the administration of fucoidan are of a confirmatory nature.
11. The results of a reduced number of white blood cells in the blood of rats and mice under the influence of *Haberlea rhodopensis* extract confirm the data obtained in rodents.
12. For the first time, an increase in the levels of IgM immunoglobulins in blood samples from rats after administration of *Ledum palustre* 9 CH and an increase in IgG after treatment with the two homeopathic products *Arnica montana* 9 CH and *Ledum palustre* 9 CH were recorded.
13. Experimentally, an increased level of IgG was found under the influence of *Aphanizomenon flos-aquae*.
14. The acute toxicity and LD50 of *Tanacetum vulgare* oil after intraperitoneal administration in rats were determined for the first time, which is relevant for future experimental studies of the plant's oil.
15. Experimental programs for electrofield stimulation to a specific neuromuscular unit (rat – n. intercostalis - m. transversus abdominis) for initiation of supramaximal muscle stimulation were optimized.
16. The lack of myorelaxant effect of etifexine was established with in vivo and in vitro experiments, and the influence of the drug on the contractile activity of striated muscles under indirect (nerve) and direct (muscle) stimulation was analyzed, and an explanation was given for the observed effects of receptor level.

17. The results of the experimental study of etifoxine prove that the drug does not worsen the processes of learning and memory, and confirm the data of clinical studies.
18. The recorded data on the neuroprotective effect of etifoxine in a model of diazepam-induced amnesia could be used in the treatment of neurotic patients with a view to reducing the ADR of benzodiazepines on memory and potentiating their anxiolytic effect.
19. A reduction in the negative effect of diazepam on locomotor activity was found when it was combined with etifoxine.
20. The ED₅₀ of oral pregabalin versus pentylenetetrazole seizure in rats was established for the first time.
21. The established lack of myorelaxant effect of pregabalin on skeletal muscles is its advantage over other antiepileptic and anxiolytic drugs.
22. The results for the analgesic effect of pregabalin, both in nociceptive pain and in neuropathic pain in chemotherapy-induced peripheral neuropathy, are confirmatory.
23. The Shuttle box active learning method is suitable for studying the influence of retigabine on the cognitive functions of intact rats and those with a PTZ-kindling model.
24. The mechanical paw pressure test is not informative enough to determine the analgesic effect of retigabine.
25. The EC₅₀ of retigabine on guinea pig gastric smooth muscle was established for the first time.
26. The scientifically sound muscle relaxant effect of retigabine explains the most commonly reported ADRs of this antiepileptic product in clinical trials, namely fatigue and weakness.
27. The obtained results for anti-inflammatory, anti-hyperalgesic effect and antagonistic activity towards histamine H₁ receptors of TASSER agonist denatonium benzoate can be used in the search for new drugs with anti-inflammatory and analgesic effect.
28. The spray drying method is more promising and is more suitable for obtaining polymeric microparticles with enalapril maleate with successful masking of its bitter taste, which is an opportunity to develop orally dispersible tablets containing enalapril maleate and intended for children practice.

29. Aqueous extract of peat, administered as two semi-solid dosage forms – gel (included in carbopol gel) and cream (included in Viofil base, Cremer): exhibits antihyperalgesic activity in a rat model of carrageenan-induced hyperalgesia. Both peat formulations have a faster onset of action compared to the analogous dosage forms containing diclofenac.

V. Reflection (citation) of the candidate's publications in the national and foreign literature.

In scientific publications referenced in Scopus and Web of science, Vesela Kokova is cited 168 times, which shows a very good international visibility of the candidate's scientific works. The impact factor of citations and reviews is 742.023. In indicator group D the author has a total of 2365 points. 2290 points are from citations and 75 points are from reviews. 146 of the citations are in scientific publications, referenced and indexed in world-famous databases with scientific information (only Scopus and Web of science).

VI. Complex, qualitative evaluation of the teaching-methodical and teaching activities.

Mag. Pharm. Vesela Kokova, d.m. enjoys the respect of her students and colleagues. She was elected as the chief assistant and deputy head of academic work and deputy head of monitoring and measurement resources at the Department of Pharmacology, Toxicology and Pharmacotherapy. Delivers lectures, conducts practical exercises, participates in semester exam sessions and possibly scientific projects. She defended two majors. Carried out outgoing mobilities under the Erasmus program in Spain, Hungary and Slovakia. Has mastered and successfully applies experimental methods. Vesela Kokova publishes the results of her scientific activity in renowned scientific publications and the scientific indicators of ch. assistant are impressive - 4863.53 points.

VII. Critical notes and recommendations

I have no critical remarks about the candidate. I recommend that he continue his research and pass on his experience and knowledge to his students and interns.

VIII. General assessment of the applicant's compliance with the minimum national requirements under Art. 2b, para. 2 and 3, respectively, to the requirements under Art. 2b, para. 5 of the ZRASRB and the requirements specific to MU - Plovdiv by

direction and for units without clinical activity, defined in the Regulations for Academic Development at the Medical University - Plovdiv.

Mag. Pharm. Vesela Kokova, d.m. fully covers the requirements of the RSASR, the Regulations for its implementation and the Regulations for the development of the academic staff at the Medical University of Plovdiv for the occupation of the academic position "Associate Professor".

IX. Conclusion - meets / does not meet the mandatory and specific conditions and scientometric criteria - for the academic position "ASSOCIATE PROFESSOR".

Having examined the materials provided to me by mag. Pharm. Vesela Kokova, MD, I believe that they fully meet the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Rules for its Application and the Rules for the Development of the Academic Staff at the Medical University - Plovdiv and the criteria laid down therein for occupying the academic position "associate professor".

I give my positive assessment for the choice of mag. Pharm. Vesela Kokova, d.m. for associate professor in the field of higher education 7. Health care and sports, professional direction 7.1 Medicine at the department "Pharmacology, toxicology and pharmacotherapy" for the teaching of Bulgarian and English in the discipline "Pharmacology / incl. pharmacokinetics and chemotherapy/ and I recommend the respected members of the Scientific Jury to vote positively for her selection.

04.12.2023

Varna

Заличено на основание
Чл.5 §1, 6."В" Регламент (ЕС)2016/679



Prof. Dr. Snezha Zlateva.MD