REVIEW

From Assoc. Prof. Dr. Reneta Slavova Gevrenova,
Faculty of Pharmacy, Medical University-Sofia

of the materials submitted in the competition
for the academic position Professor in the Institute of organic chemistry with Centre of Phytochemistry**,** Bulgarian Academy of Sciences
Higher education area 4. Natural sciences, mathematics and informatics,
Professional field 4.2. Chemical sciences
(Bioorganic chemistry, chemistry of natural and physiologically active compounds)

In the competition for "Professor", announced in the State Gazette, issue 43 of 31. 05. 2019 and on the website of Institute of organic chemistry with with Centre of Phytochemistry (IOCCP), Bulgarian Academy of Sciences, as a candidate, participates Assoc. Prof. Dr. Antoaneta Borisova Trendafilova-Savkova from Institute of organic chemistry with with Centre of Phytochemistry**,** Bulgarian Academy of Sciences

1. General presentation of the materials

Procedure presentation and inventory of the materials received for review.

In the aforementioned competition only one candidate has submitted the application - Assoc. Prof. Dr. Antoaneta Borisova Trendafilova-Savkova from Institute of organic chemistry with with Centre of Phytochemistry**,** Bulgarian Academy of Sciences.

Assoc. Prof. Trendafilova has submitted a set of materials in accordance with the Rules for the Development of the Academic Staff of Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP), and meets the criteria of IOCCP-Bulgarian Academy of Sciences for the academic position of "Professor". Assoc. Prof. Trendafilova has applied a total of 51 publications in scientific journals as follows: habilitation with 13 publications (indicator V of the Minimum Requirements of IOCCP), together with a habilitation report; 20 publications are included in indicator G and 18 articles are involved in "other publications". A list of 25 research projects has been presented, 11 of which with international participation. Assoc. Prof. Trendafilova was a project manager in 2 projects, Bulgarian coordinator in 2 projects and participant in 21 projects. 51 scientific publications, which are outside the PhD thesis and the academic position of Associate professor, are accepted for review along with 25 research projects, and are accounted for in the final evaluation. The distribution of scientific publications from indicator V according to the relevant Q factors is as follows: Q1 - 3, Q2 - 8, Q3 - 2. Regarding indicator G, the distribution is: Q1 - 5, Q2 - 4, Q3 - 7 and Q4 - 4. Documents for participation in 25 research projects are presented as well as data on the value of 6 projects. All lists of documents are accompanied by the full text of the publications, official notes and letters of notification of the research projects.

2. General description of the candidate activity

Assessment of the scientific and applied activity

The scientific articles presented by Assoc. Prof. Trendafilova in the competition are thematically related to several areas:

1. Studies on the secondary metabolites classes from plants and their chemotaxonomic relevance.

The majority of the investigations are on the sesquiterpene lactones, well known chemotaxonomic marker in Asteraceae family. Valuable scientific studies are related to isolation and identification of new natural compounds from *Artemisia alba* (10 cyclic sesquiterpenoids), *Inula aschersoniana* var. aschersoniana (4 new pseudoguaiane-type derivatives.), *I. oculus-christi* (6 sesquiterpene lactones), *Anthemis rumelica* (2 guaiane-type derivatives). It's worth noting the investigations on *Jurinea tzar-ferdinandii* resulting in the isolation of 6 sesquiterpene lactones with original structure. The second group of studies deals with the essential oil content of aromatic plants belonging to Asteraceae and Lamiaceae. In-depth study have been performed on *Artemisia alba* morphotypes; for the first time, essential oil composition from Bulgarian population of *Inula oculus-christi* has been studied as well as volatile compounds in samples with Bulgarian provenance from *Inula aschersoniana* var. aschersoniana and *I. britannica*. I highly appreciate the studies on the essential oil composition from native plants and cultivar of *Sideritis scardica*. Concerning the phenolic compounds, a novel flavonol glycoside has been discovered in *Alchemilla* species. With this respect, quantification of total flavonoids and tannins has been performed in *in vitro* and *ex situ* cultures from *Alchemilla mollis, A. achtarowii и A. jumrukczalica.* Furanocoumarin composition has been studied in *Heracleum* species (Apiaceae).

2. Phytochemical profiling and determination of individual compounds for optimization of *in vitro*/*in vivo* cultivation or assessment of the impact of environmental conditions.

This area in Assoc. Prof. Trendafilova's research is related to studies of terpenoids in *in vitro* cultures of *Artemisia alba*, as well as phenolic compounds in *in vitro, in situ, ex situ* cultures of *Centaurea davidovii* and *Alchemilla* species. It should be noted the investigations on the profiling of sesquiterpene lactones and esters in *in vitro*/*in vivo* cultures from *Arnica montana*. The impact of ecological conditions on essential oil composition of *Sideritis scardica* from different habitats has been also studied. This kind of analyses has been carried out for the extraction optimization of sesquiterpene lactones from *Inula helenium.*

3. Assessment of phytopharmaceutical potential of plant extracts and bioacive compounds.

Extracts, fractions and bioactive compounds from *Alchemilla mollis* and *A. jumrukczalic, Heracleum* species, *Artemisia alba, Inula britannica, I. oculus-christi* have been studied for radical scavenging activity and active ones have been selected. It was found relationship between the total phenolic and flavonoid content and antioxidant activity. *Heracleum* extracts inhibited acetylcholinesterase activity, while *Jurinea tzar-ferdinandii* extract/fractions/compounds revealed lipase inhibitory activity. *Arum palaestinum* extract showed cytotoxic effects towards tumor cell lines from breast cancer and hepatocellular carcinoma, as well as anti-viral effect against "bird flu". *I. oculus-christi* extracts, rich in sesquiterepene lactones, revealed selective antiproliferative effects on tumor cell lines from lung carcinoma but not on non-tumor cells.

Prof. Trendafilova participates in the competition with 51 scientific publications. All 33 publications from indicator V and G have been referenced and indexed in world-renowned databases. Concerning the group "Other publications of the author", 2 articles are in proceedings of international scientific conferences, 5 - in proceedings of national scientific conferences and seminars, and 2 - in scientific proceedings of universities. Assoc. Prof. Trendafilova presented 3 oral presentations at international conferences. All articles and reports are in English. Assoc. Prof.

Trendafilova is the first author in 13 publications from indicator V and G, and in 9 of them - the second author. She is corresponding author in 12 publications from indicator V. In all scientific articles, the candidate's contribution is in the field of secondary metabolite chemistry.

Assessment of educational and pedagogical activity

Assoc. Prof. Trendafilova was a scientific consultant for one PhD thesis, supervisor of 3 diploma thesis and mentor in two projects in the frame of the Student "Practices program".

Contributions (scientific, applied) and citations.

According to the presented habilitation report, the scientific contributions of Assoc. Prof. Trendafilova are result of interdisciplinary research and can be considered in the following main trends:

1. Phytochemical investigations of medicinal plants and/or unexplored taxa.

These investigations are connected mainly with isolation and structure elucidation of sesqui-, di- and triterpenoids, flavonoids, coumarins, furanocoumarins and phenolic acids from plants of families such as Asteraceae, Rosaceae, Apiaceae and Araceae. More than 140 individual compounds are isolated using modern chromatographic techniques, 24 of them were new natural compounds identified by spectral methods (^{1}H, ^{13}C NMR, ^{1}H-^{1}H COSY, ^{1}H -^{13}C HSQC, ^{1}H -^{13}C HMBC, NOESY, UV, IR и MS).

This direction is related to studies on sesquiterpene lactones and phenolic compounds in species from Asteraceae family (*Artemisia alba*, *Inula aschersoniana* var. aschersoniana, *I. helenium*, *I. britannica*, *I. oculus-christi*, *Anthemis rumelica*, *Jurinea tzar-ferdinandii*, *Centaurea davidovii).* New natural compounds were identifiend by spectral methods together with known ones (publications N30, 35, 53, 56, 57, 59, 64, 69, 73, 74, 75). It's worth noting that for the first time the Balkan endemic *Jurinea tzar-ferdinandii* (75) has been studied as well as Bulgarian endemic *Centaurea davidovii* (59), *Anthemis rumelica* (35). Investigations have contributed to the chemotaxonomy of the genera *Artemisia, Inula, Jurinea, Anthemis.* In this regard, flavonoids from genus *Alchemilla* (Rosaceae) have been studied and for the first time secondary metabolites have been characterized in *A. mollis* and Bulgarian endemic *A. achtarowii* и *A. A. jumrukczalica* (36, 40, 65). Another class of phenolic compounds, furanocoumarins, has been examinated for the first time in the Balkan endemic *Heracleum verticillatum* and Bulgarian endemic *H. angustisectum, H. sibiricum* и *H. ternatum* (79). For the first time, the foreign species *Asterothamnus centrali-asiaticus* (Asteraceae) (53) and *Arum palaestinum* (Araceae) (68) were also subjected to phytochemical studies. Some of the works are aimed at evaluating the biological activity of extracts, enriched fractions and/or individual compounds. Antioxidant potential of *A. mollis* и *A. jumrukczalic* (65), *Heracleum* species (79), *Artemisia alba* (74), *I. britannica* (64), *I. oculus-christi* (66) have been estimated. Enzyme inhibitory activity of *Heracleum* species and *Jurinea tzar-ferdinandii* has been evaluated on acetylcholinesterase (79) and lipase (75), respectively. Cytotoxic effect of extracts from *Arum palaestinum* (68) and *I. oculus-christi* (63, 77) has been studied.

2. Investigation of essential oil composition of aromatic and medicinal plants and *in vitro* cultures.

The essential oil composition of species from Asteraceae family (*A. alba* (44 и 52), *Inula britannica* (67), *Inula aschersoniana* (71), *Inula oculus-christi* (76), Lamiaceae species (*Sideritis*

scardica (41, 48 и 50), *Panzeria lanata* (49) и *Thymus longedetatus* (80) and Apiaceae family (*Seseli rhodopeum* (42), *Seseli rigidum* (51) has been studied. More than 200 components were identified by GC and GC-MS. In addition, chemotaxonomic relationships, correlations between chemical content and ecological conditions as well as parameters of culture media in *in vitro* cultures have been assessed.

3. Comparison of different extraction techniques of sesquiterpene lactones from medicinal plants (*Inula helenium* roots (30).

Abovementioned three categories of contributions are fundamental in characterizing medicinal and unexplored plants and finding new sources of known bioactive compounds and their isolation.

4. Quantitative determination of bioactive compounds in medicinal plants

Total phenolic compounds, flavonoid and tannins, and major compounds in plant extract have been determined by spectrometric, chromatographic (GC, HPLC, etc.) and spectroscopic methods (NMR). It's worth noting the sesquiterpene profiling of *in vivo* and *in vitro* cultures from *Arnica montana* (62), analyses of phenolics in *Centaurea davidovii in vitro* cultures (59), *Alchemilla in vitro* end *ex situ* cultures (47, 54), intact plants from *Artemisia alba, Inula britannica* and *I. oculus-christi* (64, 66, 74), furanocoumarines determination in *Heracleum* species (79). This category results have not only scientific but also scientifically-applied contributions related to the conservation of rare and endangered species and biotechnological approaches in the production of secondary metabolites.

There were 250 citations of the candidate's scientific publications in the period 2010-2019, 87 of which concern the articles from the indicator V. The most cited publications are N30 (29 citations), N36 (26 citations) and N55 (20 citations). The citation report shows the importance of the candidate's contributions in optimization the extraction of sesquiterpene lactones from *Inula helenium*, as well as studies on secondary metabolites from *Alchemilla* species and *Sideritis scardica*. Among the editions citing the publications are journals of reputation such as Phytochemistry Reviews, Talanta, Journal of Ethnopharmacology, Phytochemistry Letters, Phytotherapy, Journal of functional foods. More than half of the citations of indicator V articles were noticed after 2015. The candidate's h-factor is 11.

The prospects for development of the scientific activity of Assoc. Prof. Trendafilova are related to the continuation of phytochemical studies of intact and *in vitro* cultivated medicinal plants, evaluation of their phytopharmaceutical potential, monitoring of plant substances and products. Investigations are in the frame of EC Horizon 2020 Program, the National Scientific Program "Healthy Foods for a Strong Bio-Economy and Quality of Life" and the Center for Competence for the sustainable utilization of bio-resources and waste of medicinal and aromatic plants for innovative bioactive products as well as international projects.

Prof. Trendafilova is a recognized specialist in the field of phytochemistry in Bulgaria and abroad.

4. Assessment of the personal contribution of the candidat

The scientific papers presented reflect the personal contribution of Assoc. Prof. Trendafilova in the research on secondary metabolites from medicinal and/or unexplored plants.

5. Critical comments and recommendations

I have not critical comments.

6. Personal impressions

I know Assoc. Prof. Trendafilova for few years. In her research she demonstrates a broad erudition in the field of phytochemistry. Assoc. Prof. Trendafilova shows that can balance her precision in the experiments with keen interest in theory, revealing a marked ability to apply and use it not only for explanation of the results but also for planning new interesting experiments. Taking into consideration the excellent scientific experience and research activity of Assoc. Prof. Trendafiliva, the fact that she published more than 80 publications in field of phytochemistry, I state my very positive opinion on her abilities as a scientist.

CONCLUSION

The documents and materials presented by Assoc. Prof. Dr. Antoaneta Trendafilova meet all the requirements of Law for the Academic Staff Development of the Republic of Bulgaria, the Rules for the implementation of the Law, the Rules for the implementation of the Law in Bulgarian Academy of Sciences and the Rules of Institute of organic chemistry with with Centre of Phytochemistry. Assoc. Prof. Trendafilova submitted a sufficient number of scientific papers published after the PhD and Associate Professor position. The candidate's works contain original scientific and applied contributions that have received international recognition, as a representative part of them have been published in journals and scientific publications published by international academic publishers. Its theoretical developments have practical applicability. Assoc. Prof. Trendafilova's scientific qualification is undoubtedly.

The scientific achievements by Assoc. Prof. Trendafilova in the research fully met the specific requirements of the IOCCP-Bulgarian Academy of Sciences Rules for the application of the Law for the Academic Staff Development. After examining the materials and scientific works presented in the competition, analyzing their importance and the scientific and applied contributions involved therein, I find it appropriate to give my positive assessment and to recommend to the Scientific Jury to propose to the Scientific Board of IOCCP for selection of Assoc. Prof. Trendafilova at the academic position "Professor" in IOCCP in the professional field Chemical Sciences (Bioorganic chemistry, chemistry of natural and physiologically active substances).

04.09. 2019 Reviewer:

Assoc. Prof. Dr. Reneta Gevrenova