

Pharmaceutical chemistry

NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES CHEMISTRY AND TECHNOLOGY

ISSN 2224-5286

<https://doi.org/10.32014/2020.2518-1491.107>

Volume 6, Number 444 (2020), 127 – 133

UDC 547.99

IRSTI 31.23.23

**A.K. Umbetova¹, G.Sh. Burasheva¹, Y.S. Ikhsanov¹,
K.T. Abidkulova¹, A. Beyatli², S.N. Sagatova¹, D.K. Askanova¹**

¹Al-Farabi Kazakh National University Research Institute
of New Technologies and Materials, Almaty, Kazakhstan;

²University of Health Sciences, Department of medicinal and aromatic plants, Turkey, Istanbul.
E-mail: erbol.ih@gmail.com, gauharbur@mail.ru, alma_0875@mail.ru, samira.sagatova9@gmail.com,
karime.abidkulova@kaznu.kz, ahmet.beyatli@sbu.edu.tr, d.askanova@mail.ru

CHEMICAL RESEARCH AND BIOLOGICAL ACTIVITY OF PLANTS OF THE GENUS *ATRAPHAXIS* (*A. SPINOSA*)

Abstract. In this article identifies new sources of obtaining biological substances from plants of the genus *Atraphaxis* (*A. spinosa*) prepared in the Almaty region.

According to well - known methods, the analysis of indicators and standards of raw material quality-humidity, total ash, sulphate ash, insoluble ash in 10% hydrochloric acid-was developed and carried out.

Micro- and macroelements determined by atomic absorption spectroscopy. Analysis of the elemental composition shows that iron predominates from microelements, and sodium, potassium and calcium from macronutrients.

Conditions for obtaining a biologically active complex from the aboveground part of *Atraphaxis spinosa* developed for the first time. The optimal conditions for obtaining the complex are extractant – 50% ethanol, the ratio of extractant and raw materials – 1:8, double extraction time – 48 hours, temperature – 22 - 26 °C.

The lipophilic composition identified by chromatography-mass spectroscopy. Since lipophilic fractions of plant samples include such classes of compounds as fatty acids; mono-; di-; triglycerides, phospholipids, sterols, Sterol esters, glycolipids, fat-soluble vitamins, they can considered not only as nutritional products, but also as possible pharmacological agents. The content of lipophilic components – 26 organic compounds-was determined. It found that *A. spinosa* contains a large amount of di - (2-ethylhexyl) phthalate (54.66%) and β-sitosterol (13.11%).

A complex study of plant resources as medicinal raw materials provides for the chemical study of biologically active substances and biological screening of extracts and individual compounds obtained from plants. In most cases, the extract showed a wide range of antibacterial activity against the used strains of microorganisms.

Key words: *Atraphaxis spinosa*, mineral composition, plant quality, lipophilic composition, biological activity, Polygonaceae family.

Introduction. The family *Polygonaceae* includes about 27 genera and 800 species. Kazakhstan species of plants of the genus *Atraphaxis* have not systematically studied; therefore, the study of the chemical composition, the development of methods for the isolation of potentially biologically active substances, the study of biological activity, and the development of new drugs and herbal remedies are relevant [1].

The object of the study was *Atraphaxis spinosa* of the *Polygonaceae* family germinating in the Almaty region of the Republic of Kazakhstan [2-4].

Biologically active substances contained in the plant *Atraphaxis spinosa*. The roots of the plant contain flavonoids. In the aerial part - alkaloids. The leaves of the plant contain tannins. The flavonoids

compounds - spinoside. 3,8,3', 4'-tetrahydroxyflavon, luteolin 7-methyl ester, 3- β -L-rhamnopyranoside 3,8,3', 4'-tetrahydroxyflavone, 4'- α -D-glucofuranoside 7-luteolin 7-methyl ester, 4'- β -D-glucofuranosyl-6- β -D-glucopyranoside 7-O-luteolin methyl ester.

Materials and methods. The aerial part of *Atrapaxis spinosa*, which grows in the Almaty region, used as the object of study. In the studied object, the quantitative content of macro- and microelements was determined. The elemental composition determined by atomic absorption spectroscopy on an ASSIN instrument from Karl Zeiss [5].

For determination of the lipophilic composition of the plant, *Atrapaxis spinosa* use Soxhlet apparatus. The resulting extract was concentrated under mild conditions (water bath temperature 40-45 °C) after them, sample concentrate and analyzed on Agilent Technologies 7000 GS / MS system. Component identification carried out automatically by analogy with the known mass spectra of samples stored in the Wiley database [8-18].

Determination of the biological activity of a plant. The plant extracts used in this study coded as AS-1. The following eight strains used in this study, which included two-Gram positive strains; *Staphylococcus aureus* ATCC 6533 and *Staphylococcus epidermidis* ATCC 12228. Four-Gram negative strains, which included;

Escherichia coli ATCC 10536, *Pseudomonas aeruginosa* ATCC 15442, *Klebsiella pneumoniae* ATCC 700603, *Stenotrophomonas maltophilia* ATCC 13637, *Candida albicans* ATCC 10231. In addition to fungi strains, *Aspergillus fumigatus* ATCC 36607. All strains obtained from ATCC, Medical Microbiology Laboratory, Gazi University, and Ankara, Turkey.

As briefly, all strains cultured on tryptic soy agar (OXOID, Turkey) and aerobically incubated at 35 °C for 24 hours. Then the bacterial cultures were suspended into steril saline (0.85% NaCl) and adjusted to 0.5 McFarland turbity (10^8 cfu/mL). We used 96-well, round-bottom microtiter included negative controls (medium with plant extract only) and positive controls (medium with bacteria only) and 10 serial twofold dilutions of each eight plant extracts ranging from 0,0075-5 mg/mL with a final concentration of the bacterial cell suspension equal to 1×10^5 colony forming units per milliliter (CFU/ml). All inoculated plates incubated as mentioned above. MICs evaluated after 24 hours. MBC/MFCs performed by subculturing of 10 μ l from all wells, which exhibited no visible growth (concentration equal or higher than of MICs) on Mueller Hinton agar-free plant extract and incubated as mentioned above. MBC/MFCs evaluated after 24 hours. Tests repeated twice or more and mean values reported.

Results and its discussion. Medicinal vegetable raw materials must not contain moisture above acceptable standards, so as increased humidity, it is not necessary to store food. For the majority of species of medicinal, healthy raw materials, the acceptable moisture limit is usually 12–15%. The data presented in tables 1.

Table 1 - Benign indicators of the aerial part of *Atrapaxis spinosa*

| Index | Content, % |
|--|------------|
| Humidity | 5,7 |
| Total ash | 7,32 |
| Ash insoluble in 10% hydrochloric acid | 0,36 |
| Sulfate ash | 6,9 |

It was found that humidity corresponds to "not more than 10%", total ash - "not more than 11%", ash insoluble in 10% hydrochloric acid "not more than 1%", sulfate ash - "not more than 10%".

The study of the content of macro- and microelements in the studied sample of the aerial part of *Atrapaxis spinosa* is of interest in connection with the high biological role of individual chemical elements. In the etiology of many diseases, a significant role-played by a violation of the exchange of elements in the human body at the subcellular, tissue and organism levels. So, correlations between their imbalance and various pathologies are noted. In many diseases, the level of micro and macro elements decreases, so the search for new types of plant materials as valuable additional sources of micro and macro elements is an urgent task [3,5].

Data on the mineral composition obtained by atomic absorption analysis carried out on the material and technical basis of the center of physicochemical methods of analysis.

The results are presented in tables 2 and 3.

Table 2 - The quantitative content of trace elements in the aerial part of *Atraphaxis spinosa*

| Element | Cu | Cd | Pb | Fe | Ni | Mn |
|------------------------------|---------|---------|---------|---------|---------|---------|
| Mass in sample, mg/ml | 0.9827 | 0.5031 | 2.8704 | 92.0683 | 2.2263 | 14.2490 |
| The content in the sample, % | 0.00009 | 0.00005 | 0.00023 | 0.00915 | 0.00022 | 0.00138 |

Table 3 - The quantitative content of macronutrients in the aerial part of *Atraphaxis spinosa*

| Element | Zn | K | Na | Mg | Ca |
|------------------------------|----------|-----------|-----------|----------|----------|
| Mass in sample, mg/ml | 343.2117 | 2600.0997 | 1161.3053 | 210.0357 | 4790.358 |
| The content in the sample, % | 0.0339 | 0.260 | 1.161 | 0.021 | 0.479 |

From these tables it follows that the content of Na, K exceeds the concentration of Na +, K + in the *Atraphaxis spinosa* plant under saline conditions, and they quickly diffuse inward and easily saturate the cell sap. For halophytes, ion pumps operate in the opposite direction, pumping out excess Na +, K + cations in exchange for H + ions. The highest Ca content is also noted.

It is known that a number of trace elements that accumulate by plants play a positive role in the biosynthesis of biologically active substances. It was established that plants producing polyphenolic compounds, coumarins, vitamins, selectively absorb copper, zinc, manganese. By the quantitative content of trace elements, iron dominates in the aerial part of *Atraphaxis spinosa*. In addition, a large amount contains manganese.

The specific need of halophytes for a certain concentration and composition of ash elements serves as the scientific basis for developing methods for introducing halophytes in botanical gardens. The content of macro- and micronutrients in raw materials meets the MPC standards.

Biologically active substances from *A. spinosa* extracted with 50% ethyl alcohol in the ratio of raw solvent 1:8, at room temperature for 48 hours. The resulting extract was concentrated in the vacuum of a water-structural pump. For preliminary separation of BAS, fractional hexane extraction performed. Hexane extract was analyzed by chromatography - mass spectrometry. The data presented in table 4.

Table 4 - Lipophilic composition of the plant

| № | Name of compound | Formula | RT | Share, % |
|----|-------------------------------------|--|-------|----------|
| 1 | Tridecan | C ₁₃ H ₂₈ | 6,79 | 1,20 |
| 2 | Gibylphthalate | C ₁₆ H ₂₂ O ₄ | 20,53 | 1,15 |
| 3 | Palmitic acid | C ₁₆ H ₃₂ O ₂ | 20,63 | 1,22 |
| 4 | 9.17 - Octadecandianal | C ₁₈ H ₃₂ O | 23,98 | 3,95 |
| 5 | 2 -Nadonecanone | C ₁₉ H ₃₈ O | 26,70 | 1,44 |
| 6 | 1.21- Docosadien | C ₂₂ H ₄₂ | 28,64 | 0,56 |
| 7 | Di (2-ethylhexyl) phthalate | C ₂₄ H ₃₈ O ₄ | 30,65 | 54,66 |
| 8 | Tricosan | C ₂₃ H ₄₈ | 32,72 | 0,68 |
| 9 | α - Toxopyro B | C ₂₉ H ₅₀ O ₄ | 34,92 | 1,92 |
| 10 | Eicosan | C ₂₀ H ₄₂ | 35,50 | 1,10 |
| 11 | 4,5-Dimethyl benzenediol-1,3 | C ₈ H ₁₀ O ₂ | 37,65 | 0,48 |
| 12 | 1-Chlorheptacosan | C ₂₇ H ₅₅ Cl | 38,10 | 0,76 |
| 13 | Vitamin E | C ₂₉ H ₅₀ O ₂ | 38,60 | 0,75 |
| 14 | P- (3-methoxy-2-methyl) propanamide | C ₅ H ₁₁ NO ₂ | 38,70 | 0,50 |
| 15 | 1,3-Benzenediol 5-pentadecyl | C ₆ H ₆ O ₂ | 39,65 | 4,70 |

| | | | | |
|----|---------------------------------------|-----------------|-------|-------|
| 16 | Campester | $C_{28}H_{48}O$ | 39,79 | 0,74 |
| 17 | Stigmaster | $C_{29}H_{48}O$ | 40,20 | 1,50 |
| 18 | 2-Methyl-5- (methyl ethyl) cyclohexen | $C_{10}H_{16}O$ | 40,29 | 2,57 |
| 19 | β -Systerol | $C_{29}H_{50}O$ | 41,03 | 13,11 |
| 20 | α -Amirin | $C_{30}H_{50}O$ | 41,73 | 1,89 |
| 21 | lanosterol | $C_{30}H_{50}O$ | 42,02 | 0,50 |
| 22 | lupeol | $C_{30}H_{50}O$ | 42,10 | 2,40 |
| 23 | Stigmast-4-en- 3-one | $C_{29}H_{48}O$ | 42,90 | 0,86 |

Various derivatives of hydrocarbons of lipophilic substances of a plant of the genus *A.spinosa* were found: tridecane (1.20%), dibylphthalate (1.15%), palmitic acid (1.22%), 9,17 - octadecandianal (3.95%), 2 - nadonecanone (1.44%), 1,21-backed (0.56%), di (2-ethylhexyl) phthalate (54.66%), tricosan (1.02%), α - toxopyro B (0.90%), α - toxocipro B (1.10%), eicosan (10.48%), 4,5-dimethyl benzenediol-1,3 (0.76%), 1-chlorheptacosan (0.75%), vitamin E (0.64%), P- (3-methoxy-2-methyl) propanamide (4.70%), 1,3-benzenediol 5-pentadecyl (4.70%), campester (1.50%), stigmaster (1.89%), 2-methyl-5- (methyl ethyl) cyclohexen (2.57%), β -systerol (13.11%), α -amirin (1.89%), lanosterol (0.50%), lupeol (2.40%), stigmast-4-en- 3-one (0.86%).

It found that a large amount of *A. spinosa* contains Di - (2-ethylhexyl) phthalate (54.66%) and β -sitosterol (13.11%).

The MIC and MBC/MFC values shown in table 5 and 6.

Table 5 - Minimum Inhibitory Concentration (MIC) of various plant extracts against different strains

| Microbial strains | MIC mg/mL | |
|-----------------------|-----------|--|
| | AS-1 | |
| <i>S. aureus</i> | 0.075 | |
| <i>S. epidermidis</i> | 0.0075 | |
| <i>E. coli</i> | 0.625 | |
| <i>P. aeruginosa</i> | 0.156 | |
| <i>K. pneumonia</i> | 0.078 | |
| <i>S. maltophilia</i> | 0.156 | |
| <i>C. albicans</i> | 0.312 | |
| <i>A. fumigatus</i> | 2.5 | |

Table 6 - Minimum Bactericidal Concentration (MBC/MFC) of various plant extracts against different strains.

| Microbial strains | MBC/MFC mg/mL | |
|-----------------------|---------------|--|
| | AS-1 | |
| <i>S. aureus</i> | 0.03 | |
| <i>S. epidermidis</i> | 0.03 | |
| <i>E. coli</i> | 1.25 | |
| <i>P. aeruginosa</i> | 0.625 | |
| <i>K. pneumonia</i> | 0.312 | |
| <i>S. maltophilia</i> | 0.625 | |
| <i>C. albicans</i> | 1.25 | |
| <i>A. fumigatus</i> | >5 | |

In most cases, extracts exhibited a broad spectrum of antibacterial activity against used microbial strains. AS-1 showed the lowest MIC values (0.0075 mg/mL) with respect to *S. aureus* and *S. epidermidis*. MBC values of 0.03 mg/mL for AS-1.

Conclusion. Thus, the elemental composition and benignity of the aerial parts of the plant *Atraphaxis spinosa* studied. It established that the benignity of the plant does not exceed acceptable values.

As a result, the plant can be considered medicinal raw materials. An analysis of the elemental composition showed that Fe prevails from microelements, and Na, K and Ca from macroelements.

The lipophilic composition and biological activity of the plant was also established. It was found that a large amount of *A. spinosa* contains di - (2-ethylhexyl) phthalate (54.66%) and β-sitosterol (13.11%).

These plant extracts could be new antimicrobial agents with significant potential. This matter may be due to the materials extracted from various solvents

**А.К. Умбетова¹, Г.Ш. Бурашева¹, Е.С. Ихсанов¹,
К.Т. Абидкулова¹, А. Бейтали², С.Н. Сагатова¹, Д.К. Асканова¹**

¹Әл-Фараби атындағы Қазақ ұлттық университеті

Жаңа технологиялар мен материалдар ғылыми-зерттеу институты, Алматы, Қазақстан;

²Денсаулық ғылымдары университеті, Стамбул, Түркия

ATRAPHAXIS (A.SPINOSA) ТЕКТЕС ӨСІМДІГІН ХИМИЯЛЫҚ ЗЕРТТЕУ ЖӘНЕ БИОЛОГИЯЛЫҚ БЕЛСЕНДІЛІГІ

Аннотация. Мақалада Алматы облысында дайындалған *Atraphaxis (A. spinosa)* текстес өсімдікten биологиялық зат аудын жаңа көзі айқындалды. Белгілі әдістер бойынша шикізат сапасының көрсеткіші мен нормалары – ылғалдылық, жалпы күл, сульфатты күл ері 10% тұз қышқылында ерімейтін күл анықтау саралтамалары жүргізілді. Атомдық-абсорбциялық спектроскопия әдісімен микро және макроэлементтік құрамы анықталды. Элемент құрамын талдау микроэлементтерден темір басым, ал макроэлементтерден натрий, калий және кальций басым екенін көрсетеді.

Алғаш рет *Atraphaxis spinosa* жерүсті белгілінен биологиялық белсененді кешенді алу жағдайы жасалды. Кешен алу үшін анықталған онтайлы жағдайлар: экстрагент – 50% этанол, экстрагент пен шикізаттың аракатынасы – 1:8, екіреттік экстракция уақыты – 48 сағат, температура – 22-26 °C.

Хромато-масс-спектроскопия әдісімен липофильді құрам анықталды. Өсімдік үлгілерінің липофильді фракциясында май қышқылы сиякты қосылыс кластары, яғни моно-, ди-, триглицерид, фосфолипид, стерол, стерол эфири, гликолипид, майда еритін витаминдер кіретіндіктен оларды тек қоректік зат ретінде ғана емес, фармакологиялық агенттер ретінде де қарастыруға болады. Липофильді компоненттер құрамы анықталды, яғни ол – 26 органикалық қосылыс. *A. spinosa* құрамында көп мөлшерде ди- (2-етилгексил) фталат (54,66%) және β-ситостерол (13,11%) бар екені анықталды.

Дәрілік шикізат ретінде өсімдік ресурстарын кешенді зерттеу биологиялық белсененді заттарды химиялық зерттеуді, сондай-ақ өсімдіктерден алынған экстрактілер мен жеке қосылыстардың биологиялық скринингін жүргізуі көздейді. Көп жағдайда экстракт қолданылған микроорганизмдер штамына қарсы антибактериалды белсенділіктің көң спектрін көрсетті.

Түйін сөздер: *Atraphaxis spinosa*, минералды құрам, өсімдік сапасы, липофильді құрам, биологиялық белсенділік, Polygonaceae тұқымдасты

**А.К. Умбетова¹, Г.Ш. Бурашева¹, Е.С. Ихсанов¹,
К.Т. Абидкулова¹, А. Бейтали², С.Н. Сагатова¹, Д.К. Асканова¹**

¹Казахский национальный университет имени аль-Фараби

Научно-исследовательский институт новых технологий и материалов, Алматы, Казахстан;

²Университет наук о здоровье, Кафедра лечебных и душевых растений, Турция, Стамбул

ХИМИЧЕСКОЕ ИССЛЕДОВАНИЕ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ РАСТЕНИЙ РОДА ATRAPHAXIS (A.SPINOSA)

Аннотация. В данной статье определены новые источники получения биологических веществ из растений рода *Atraphaxis (A. spinosa)*, заготовленных в Алматинской области.

По известным методикам отработаны и проведены анализы показателей и норм качества сырья: влажность, общая зола, сульфатная зола, зола нерастворимая в 10% -ной соляной кислоте.

Методом атомно-абсорбционной спектроскопии установлены микро- и макроэлементы. Анализ элементного состава показывает, что из микроэлементов преобладает железо, а из макроэлементов – натрий, калий и кальций.

Впервые разработаны условия получения биологически активного комплекса из надземной части *Atrapaxis spinosa*. Оптимальными условиями для получения комплекса являются: экстрагент – 50% этанол, соотношение экстрагента и сырья – 1:8, время двукратной экстракции – 48 часа, температура – 22 - 26 °C.

Методом хромато-масс-спектроскопией идентифицирован липофильный состав. Поскольку липофильные фракции растительных образцов включают такие классы соединений, как жирные кислоты; моно-; ди-; триглицериды, фосфолипиды, стерины, эфиры стеринов, гликолипиды, жирорастворимые витамины, можно рассматривать их не только в качестве питательных продуктов, но и как возможные фармакологические средства. Установлено содержание липофильных компонентов – 26 органических соединений. Выявлено, что в составе *A.spinosa* большое количество содержится ди - (2-этилгексил) фталата (54,66%) и β-ситостерола (13,11%).

Комплексное исследование растительных ресурсов как лекарственного сырья предусматривает и химическое изучение биологически активных веществ, и проведение биологического скрининга экстрактов и индивидуальных соединений, полученных из растений. В большинстве случаев экстракт проявлял широкий спектр антибактериальной активности в отношении использованных штаммов микроорганизмов.

Ключевые слова: *Atrapaxis spinosa*, минеральный состав, доброкачественность растения, липофильный состав, биологическая активность, семейство *Polygonaceae*.

Information about authors:

Ikhsanov Y.S., PhD Department of Chemistry and Chemical Technology of the Al-Farabi Kazakh National University, Kazakh National University, e-mail: erbol.ih@gmail.com, <https://orcid.org/0000-0003-4640-9584>;

Umbetova A.K., Candidate of chemical Sciences, faculty of chemistry and chemical technology, al-Farabi Kazakh national University, El. mail: alma_0875@mail.ru, <https://orcid.org/0000-0001-9879-5398>;

Burasheva G.Sh., Doctor of Science professor, Department of Chemistry and Chemical Technology of the Al-Farabi Kazakh National University, e-mail: gauharbur@mail.ru, <https://orcid.org/0000-0003-2935-3531>;

Abidkulova K.T., Candidate of science Department of chemistry and chemical technology, al-Farabi Kazakh national University, akniyettashimbetova@mail.ru, <https://orcid.org/0000-0001-7916-4531>;

Beyatli A., Professor of ²University of Health Sciences, Department of medicinal and aromatic plants, ahmet.beyatli@sbu.edu.tr, <https://orcid.org/0000-0003-1847-8822>;

Sagatova S.N., Master's student Department of chemistry and chemical technology, al-Farabi Kazakh national University, samira.sagatova9@gmail.com, <https://orcid.org/0000-0001-7078-8938>;

Askanova D.K., Master's student Department of chemistry and chemical technology, al-Farabi Kazakh national University, akniyettashimbetova@mail.ru, <https://orcid.org/0000-0002-2230-6938>

REFERENCES

- [1] Zengin G., Sarikurkcu C., Aktumsek A., Ceylan R., & Ceylan O. (2014). A comprehensive study on phytochemical characterization of *Haplophyllum myrtifolium* Boiss. endemic to Turkey and its inhibitory potential against key enzymes involved in Alzheimer, skin diseases and type II diabetes. *Industrial Crops and Products*, 53, 244–251. doi:10.1016/j.indcrop.2013.12.043
- [2] Oscanov B. S., Ikhsanov Y. S., Litvinenko Yu. A., Adekenov S. M., Burasheva G. Sh., Biologically active substances from plant sudaeda vera and their anestizing activity N e w s of the national academy of sciences of the republic of kazakhstan series of biological and medical ISSN 2224-5308 [https://doi.org/10.32014/2018.2518-1629.8 V. 5, Number 329 \(2018\), 63 – 66](https://doi.org/10.32014/2018.2518-1629.8 V. 5, Number 329 (2018), 63 – 66).
- [3] Aitkulova R.E., Abubakirova A.A., Kudasova D.E., Kaldybekova G.M. (2016) Role of medicinal plants from south-kazakhstan region for addition into livestock's fodder. N e w s of the national academy of sciences of the republic of kazakhstan series of biological and medical 314: 155–158 [https://doi.org/10.32014/2018.2518- 1629 \(in Eng\).](https://doi.org/10.32014/2018.2518- 1629 (in Eng).)
- [4] Aitkulova RE, Abubakirova AA, Kudasova DE, Kaldybekova GM (2016) Role of medicinal plants from south-kazakhstan region for addition into livestock's fodder. N e w s of the national academy of sciences of the republic of kazakhstan series of biological and medical 314: 155 – 158 [https://doi.org/10.32014/2018.2518- 1629 \(in Eng\).](https://doi.org/10.32014/2018.2518- 1629 (in Eng).)
- [5] Hamdi, A., Majouli, K., Vander Heyden, Y., Flamini, G., & Marzouk, Z. (2017). Phytotoxic activities of essential oils and hydrosols of *Haplophyllum tuberculatum*. *Industrial Crops and Products*, 97, 440–447. doi:10.1016/j.indcrop.2016.12.053
- [6] Al-Rehaily A. J., Alqasoumi S. I., Yusufoglu H. S., Al-Yahya M. A., Demirci B., Tabanca N., ... Baser K. H. C. (2014). Chemical Composition and Biological Activity of *Haplophyllum tuberculatum*Juss. Essential Oil. *Journal of Essential Oil Bearing Plants*, 17(3), 452–459. doi:10.1080/0972060x.2014.895211
- [7] Eissa T. F., González-Burgos E., Carretero M. E., & Gómez-Serranillos M. P. (2013). Biological activity of HPLC-characterized ethanol extract from the aerial parts of *Haplophyllum tuberculatum*. *Pharmaceutical Biology*, 52(2), 151–156. doi:10.3109/13880209.2013.819517

- [8] Tekin M., Eruygur N. (2016). The structural studies on the medicinal plant *Haplophyllum telephioides*. *Revista Brasileira de Farmacognosia*, 26(5), 544–552. doi:10.1016/j.bjp.2016.05.007
- [9] Debouba M., Khemakhem B., Zouari S., Meskine A., & Gouia H. (2014). Chemical and Biological Activities of *Haplophyllum tuberculatum* Organic Extracts and Essential Oil. *Journal of Essential Oil Bearing Plants*, 17(5), 787–796. doi:10.1080/0972060x.2014.958545
- [10] Hamdi A., Viane J., Mahjoub M. A., Majouli K., Gad M. H. H., Kharbach M., ... Heyden Y. V. (2018). Polyphenolic contents, antioxidant activities and UPLC-ESI-MS analysis of *Haplophyllum tuberculatum* A. Juss leaves extracts. *International Journal of Biological Macromolecules*, 106, 1071–1079. doi:10.1016/j.ijbiomac.2017.08.107
- [11] Rasulova K. A., Kodirova D. R., Bobakulov K. M., Abdullaev N. D. (2015). Griffithine, a New Furanoquinolone Alkaloid from *Haplophyllum griffithianum*. *Chemistry of Natural Compounds*, 51(4), 743–745. doi:10.1007/s10600-015-1398-1
- [12] Azadi, B., Khaef, S., & Ziarati, P. (2014). Chemical composition of *Haplophyllum villosum*(M. B.) G. Don Essential Oil. *Journal of Essential Oil Bearing Plants*, 17(6), 1161–1164. doi:10.1080/0972060x.2014.958556
- [13] ULUKUŞ D., TUGAY O., & CELEP F. (2016). Morphology, Anatomy and Palynology of Turkish endemic species *Haplophyllum myrtifolium*, *H. vulcanicum* & *H. megalanthum* (Rutaceae) and their systematics implications. *Phytotaxa*, 247(3), 197. doi:10.11646/phytotaxa.247.3.3
- [14] Cao J., Pang X., Guo S., Wang Y., Geng Z., Sang Y., ... Du S. (2019). Pinene-rich essential oils from *Haplophyllum dauricum* (L.) G. Don display anti-insect activity on two stored-product insects. *International Biodeterioration & Biodegradation*, 140, 1–8. doi:10.1016/j.ibiod.2019.03.007
- [15] Hamdi A., Majouli K., Abdelhamid A., Marzouk B., Belghith H., Chraief I., ... Heyden Y. V. (2018). Pharmacological activities of the organic extracts and fatty acid composition of the petroleum ether extract from *Haplophyllum tuberculatum* leaves. *Journal of Ethnopharmacology*, 216, 97–103. doi:10.1016/j.jep.2018.01.012
- [16] Azadi B., & Khaef S. (2015). Volatile constituents of *Haplophyllum buhsei* Boiss. flowering aerial parts. *Bulletin of the Chemical Society of Ethiopia*, 29(2), 327. doi:10.4314/bcse.v29i2.15
- [17] Aberrane S., Djouahri A., Djerrad Z., Saka B., Benseradj F., Aitmoussa S., ... Boudarene, L. (2018). Changes in essential oil composition of *Haplophyllum tuberculatum* (Forsk.) A. Juss. aerial parts according to the developmental stage of growth and incidence on the biological activities. *Journal of Essential Oil Research*, 1–21. doi:10.1080/10412905.2018.1511483
- [18] Rasulova K. A., Bobakulov K. M., Eshonov M. A., Abdullaev N. D. (2019). Pedicine, a New Alkaloid from *Haplophyllum pedicellatum*. *Chemistry of Natural Compounds*. doi:10.1007/s10600-019-02784-7