DOI 10.1007/s11094-023-02853-w
Pharmaceutical Chemistry Journal, Vol. 57, No. 1, April, 2023 (Russian Original Vol. 57, No. 1, January, 2023)

SECONDARY METABOLITES OF *Oplopanax elatus*: POSSIBILITIES FOR STANDARDIZATION OF A MULTIPHYTOADAPTOGEN FOR PREVENTIVE ONCOLOGY

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 57, No. 1, pp. 29 – 36, January, 2023.

Original article submitted September 1, 2022.

An herbal formulation of a multiphytoadaptogen (MPA) developed at the N. N. Blokhin Cancer Center and containing phytocomponents from *Oplopanax elatus* Nakai has been studied in preclinical and clinical trials for preventive oncology. Secondary metabolites were identified in the extract of rhizomes and roots of *O. elatus* and in the MPA pharmaceutical composition using high performance liquid chromatography-mass spectrometry (HPLC-MS/MS). Compounds identical to ginsenosides Rd and Re (tetracyclic triterpene saponins from *Panax ginseng*) and araloside C and stipuleanoside R2 (pentacyclic triterpene saponins, oleanolic acid derivatives, from *Aralia mandshurica*) were identified in the MPA and in the extract of rhizomes and roots of *O. elatus*. The spectra of biological activity of ginsenosides Rd and Re, araloside C, and stipuleanoside R2 were analyzed *in silico* using the PASS computer program. According to published data and *in silico* analysis, the activities of ginsenosides Rd and Re, araloside C, and stipuleanoside R2 correspond to properties previously confirmed in the MPA studies for preventive oncology.

Keywords: *Oplopanax elatus*, ginsenosides Re and Rd, araloside C, stipuleanoside R2, HPLC-MS/MS, multiphytoadaptogen, preventive oncology, *in silico*, PASS, PharmaExpert.

Issues with standardization and rationalization of the pharmacological activity of multicomponent phytoadaptogens considering their chemical composition are an active research area [1 – 6].

A multiphytoadaptogen (MPA) pharmaceutical composition for preventive oncology and gerontology has been developed at N. N. Blokhin National Medical Research Center of Oncology [7]. The MPA contains components of extracts from 40 official plants, including adaptogens from ginseng, aralia, *Eleutherococcus*, *Rhodiola roseus*, *Oplopanax elatus*, and *Schizandra*. The MPA was shown to be effective for preventive oncology, which is known to encompass primary (prevention of genesis or chemoprevention), secondary (prevention of recidivism and tumor metastasis), and tertiary prevention of oncological diseases (prevention of chemotherapy and beam side effects) [3]. Drugs for preventive oncology should absolutely possess antitumor and protective effects as the main properties. Antimutagenic (which is important for primary prevention of cancer), antitumor (important for secondary prevention), radioprotective, hormone-modulating, antioxidant, neuroprotective, and immunomodulating including adhesiogenic and interferonogenic effects of the MPA (important for tertiary prevention of cancer) have been found in experimental and clinical research [7 – 18]. The effective-

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ness of the MPA is undoubtedly due to the complex of biologically active compounds (BACs) included in it.

Research on the determination of the BACs in the MPA components is being conducted to assess the possibilities for quality control and standardization of the MPA. For example, polyphenolic compounds, essential oils, amino acids, and vitamins were found in the MPA using reversed-phase HPLC with UV detection, GC-MS, and NMR spectroscopy [19 – 21]. In addition, HPLC in combination with tandem mass spectrometry (HPLC-MS/MS) identified the main BACs among the MPA components, particularly ginseng and aralia, as triterpene saponins, i.e., ginsenosides Rb1, Rb2, Rc, Rd, Rg1, Rg2, Re, Rf, and Ro and aralosides A, B, and C [22, 23]. The phenylethanolglycoside salidroside, phenylpropanoid glycosides rosavin and rosarin, monoterpene glycoside rosiridin, and flavonoid rhodionin were determined as constituents of *R. rosea* BACs [24]; the phenylpropanoid eleutheroside B and the lignan eleutheroside E, of *Eleutherococcus* [25]; and the lignans schizandrin (schizandrol A) and schizantherin A (gomisin C), from *Schizandra* [26].

The next stage in the analysis of the constituent composition of the MPA was a determination of the BACs in the extract of rhizomes and roots of *O. elatus*, which is included in the MPA, using HPLC-MS/MS. This method has excellent specificity and high accuracy that enables the determination of trace amounts of compounds.

O. elatus Nakai (Araliaceae) is a deciduous thorny bush with long, creeping, woody rhizomes. Its lifespan is >300 years although it grows very slowly by 5 – 10 cm per year. The plant is like ginseng with respect to its medicinal activity although weaker. It contains a complex of BACs with useful properties. It is distributed in forests of the Far East and Ussuriysk Territory of Russia. It grows in fir and fir-birch forests and is shade tolerant. It is endemic to Primorsky Territory and is protected, i.e., included in the Red Book of Russia and Primorsky Territory. *O. elatus* is dying out because of overharvesting for medicinal purposes, forest fires, and low seed productivity. The biologically active complex of the plant includes triterpene saponins such as echinacosides, flavonoid glycosides, coumarins, lignans, essential oil, and resinous substances. However, the chemical composition of *O. elatus* is poorly studied. It possesses adaptogenic, immunomodulating, cardiotonic, neuroprotective, hormone-modulating, antidiabetic, and diuretic activity. The infusion of *O. elatus* is used for heart failure, physical and mental overexertion, and erectile dysfunction in men [27].

The aim of the present study was to determine the BACs of *O. elatus* in the MPA using HPLC-MS/MS and to assess the biological activity profile of the identified phytoconstituents using *in silico* analysis.

EXPERIMENTAL PART

Two samples were investigated in the work, i.e., the MPA and extract of rhizomes and roots of *O. elatus* included in the MPA composition. Samples of extracts were obtained using certified raw material and the same extraction technology, i.e., specific weight of raw material, extraction temperature and time regimes, extractant composition, and raw-material:extractant ratio.

An MPA sample was mixed with MeOH (1:2 ratio) and centrifuged for 5 min at 13,000 rpm. The supernatant liquid was passed through a 0.22-μm filter and centrifuged at 13,000 rpm for 1 min.

An aliquot (1 mL) of the *O. elatus* extract was evaporated to dryness in a Concentrator 5301 rotary evaporator (Eppendorf, Germany) at 30°C. The residue was dissolved in MeOH (100 μL) and centrifuged at 13,000 rpm for 1 min.

Chromatographic analysis of samples used a TSQ Vantage triple quadrupole mass spectrometer (Thermo Scientific TSQ series) connected to an Accela HPLC.

The analytical chromatography conditions were ACQUITY UPLC BEH C18 column (2.1 × 100 mm, 1.7 μm; Waters); mobile phase composition: phase A (100% H_2O) + formic acid (FA, 0.1%) and phase B (Me_2CO 95%, H_2O 5%, FA 0.1%).

Gradient elution was used to analyze the extracts (%B): 0 – 68 min (0 – 60%), 68 – 70 min (60 – 100%), 70 – 75 min (100%), and 75 – 80 min (0%). Samples (5 μL) were injected into a 25-μL loop (mobile phase, 20 μL). The flow rate was 450 μL/min.

Electrospray ionization was used. The conditions were negative polarity, spray capillary potential 4 kV, spray gas 60 psi, bypass gas 15 rel. units, capillary temperature 270°C. Total ion spectra were scanned with selected-ion monitoring in the range 150 – 1500 Da and scan time 0.1 sec.

Mass spectra were obtained by direct sample introduction through a syringe at 5 μL/min. The gas pressure in the impact chamber was 0.9 Torr. The potential in the impact chamber was selected separately for each compound.

Analysis *in silico*. Spectra of antitumor activity of *O. elatus* phytoconstituents were calculated using the PASS Refined 2022 software. The PASS software is based on a naive Bayesian algorithm and representation of structures as MNA descriptors [28]. The used version of the PASS software allowed the prediction of 1957 types of biological activity with an average accuracy of 97% [29]. The set of predicted activities was limited in the present work to 38 antitumor effects and 54 mechanisms of action associated with them.

The input data for PASS were structures of the compounds given in MOL or SDF format [30]. The result of the prediction was a list of biological activities with the calculated estimates Pa (probability of a compound being assigned to an active class) and Pi (probability of a compound being assigned to an inactive class) for each analyzed medici-

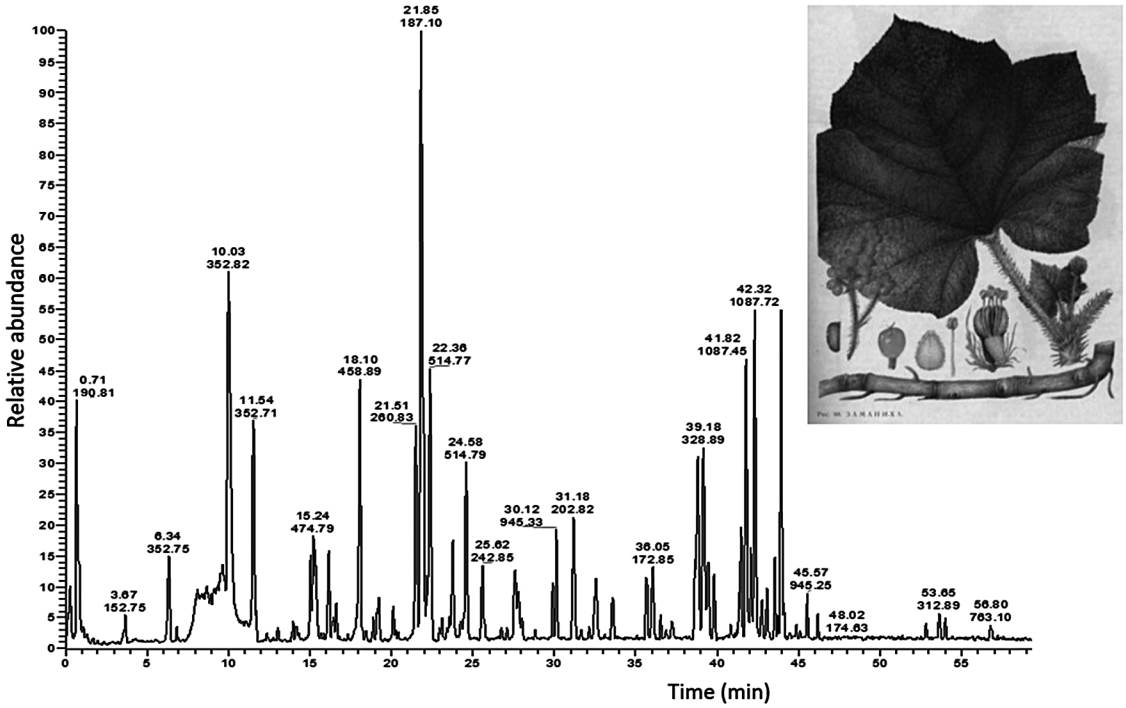


Fig. 1. Chromatogram of total ion current of *O. elatus* Extract.

nal-like compound. All activities for which the calculated Pa exceed the Pi value were considered probable [28].

Additive/synergistic activity and possible drug(drug interactions of the studied chemical compounds were analyzed using the PharmaExpert software [31], which is based on a knowledge base containing information on >15,000 known interactions between pharmacological effects and mechanisms of action of pharmacological compounds.

RESULTS AND DISCUSSION

A review of the literature showed that the chemical composition of *O. elatus* was poorly studied. Specific data on the main BACs included in it had not been published.

A chromatogram of the extract of *O. elatus* included in the MPA composition was taken in total ion scanning mode to study the main BACs (Fig. 1).

TABLE 1 lists the results of tandem mass spectrometric analysis of *O. elatus* extract (R_t, *m*/*z* of the pseudomolecular ion and its fragments) and the molecular mass of the compound.

TABLE 1 shows that the studied compounds from *O. elatus* formed ion-adducts [M + FA (H](with FA included in the mobile phase. One of the peaks with *m*/*z* 945.34 and retention time R_t = 30.12 min corresponded to a compound identical to ginsenoside Re from ginseng. A peak with *m*/*z* = 945.25 and R_t = 45.6 min corresponded to a compound identical to ginsenoside Rd, also from ginseng. Compounds giving peaks with *m*/*z* 1087.5 and R_t = 41.8 and 42.3 min had the same experimental characteristics (retention times and MS/MS spectra) as araloside C and stipuleanoside R2 from aralia extract. The extract of *O. elatus* probably contained the same compounds as in ginseng and aralia extracts or isomers very similar to them.

Thus, the main BACs of *O. elatus* were not specific compounds for this extract but compounds similar to those from other adaptogens, i.e., ginseng and aralia. In turn, these were ginsenosides Re and Rd (tetracyclic triterpene saponins) and araloside C and stipuleanoside R2 (pentacyclic triterpene saponins). They were also identified in *O. elatus* extract.

The chromatogram of the MPA was analyzed for content of *O. elatus* BACs knowing the retention time and *m*/*z* value of the main molecular ion. Figure 2 shows the chromatogram of the MPA in total ion scanning mode.

Chromatograms of the MPA obtained under the same conditions as that for *O. elatus* extract were analyzed by detecting separate ions corresponding to the main molecular ions of *O. elatus* ions (based on data given in Table 1). The sought ions were identified in the MPA chromatogram and the presence of ginsenosides Re and Rd, araloside C, and stipuleanoside R2 in the composition was confirmed by the analysis.

Results of analysis *in silico* of the antitumor effects of *O. elatus* phytoconstituents are given in Fig. 3.

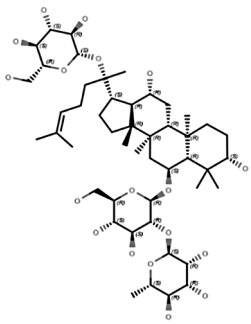
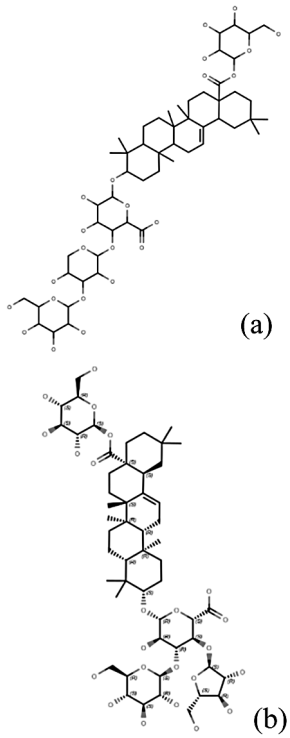
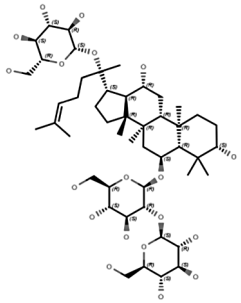
Figure 3 shows that 26 antitumor effects were predicted for *O. elatus* compounds with positive Pa – Pi values. Of these, 15 were predicted with Pa – Pi values >0.5 for at least one of the studied compounds. Table 2 lists the compounds

for which antitumor effects were predicted with Pa – Pi values >0.7.

TABLE 2 shows that an antitumor (Antineoplastic) effect (lung cancer) was predicted for four of the studied compounds with Pa – Pi values >0.7. Antineoplastic effects (ovary cancer, melanoma, and breast cancer) with an analogous threshold were predicted for araloside C and stipuleanoside R2.

The most probable mechanisms of action associated with the antitumor effects were established by us using the PharmaExpert software. Table 3 gives the corresponding results.

TABLE 1. Experimental Data for Extract of *Oplopanax elatus* Nakai

Compound	Structural formula	R_t, min	*m*/*z*
MM 947.2 Compound identical to ginsenoside Re ($C_{48}H_{82}O_{18}$)		30.12	945.34 $[M – H]^-$ 783.19 $[M – H – Glc]^-$ 621.6 $[M – H – 2Glc]^-$ 459.4 $[Aglycone – H]^-$
MM 1089 Compound identical to araloside C (a) and stipuleanoside R2 (b) ($C_{53}H_{84}O_{23}$)		41.82 42.32	1087.45 $[M – H]^-$ 954.84 925.24 $[M – H – Glc]^-$ 757.59 731.09 661.3 551.16 523.61 454.95 $[Aglycone – H]^-$
MM 947.2 Compound identical to ginsenoside Rd (C48H82O18)		45.6	945.25 $[M – H]^-$ 783.19 $[M – H – Glc]^-$ 621.6 $[M – H – 2Glc]^-$ 459.4 $[Aglycone – H]^-$

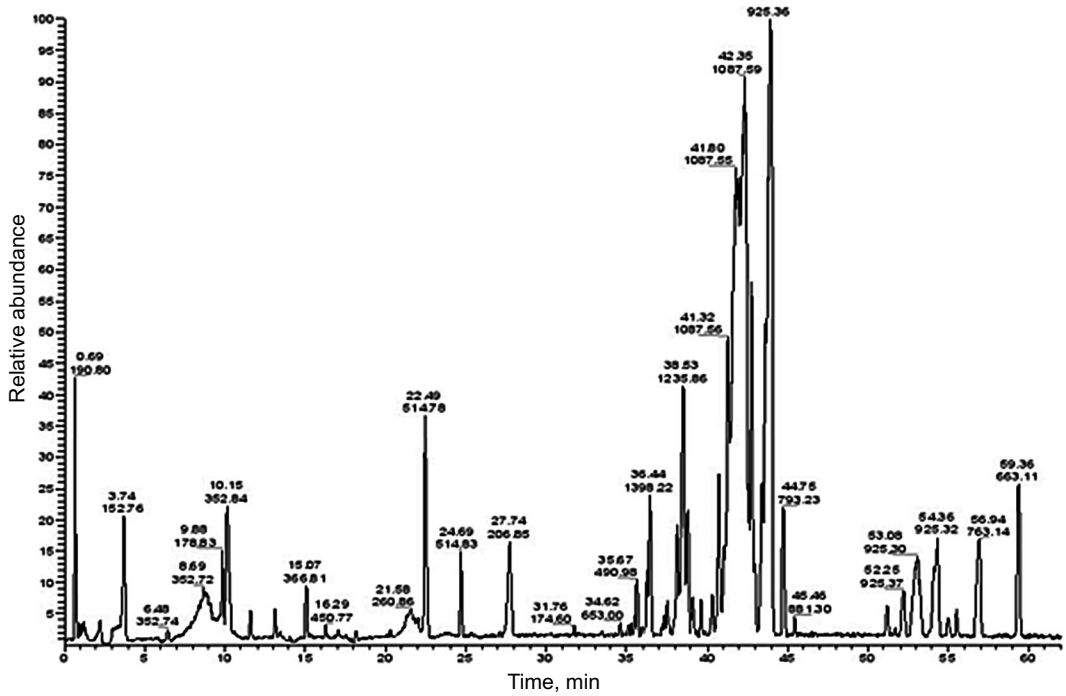


Fig. 2. Chromatogram of the MPA in total ion current mode.

TABLE 3 shows that two mechanisms of action, i.e., inhibition of transcription factor NF-κB and agonistic activity for apoptosis, were predicted for all studied compounds with threshold Pa – Pi > 0.9. Also, antioxidant activity was predicted for ginsenosides at this threshold. Four mechanisms of action were predicted for threshold Pa – Pi > 0.6. They included inhibition of tumor necrosis factor alpha release, stimulation of caspase 3, stimulation of AMP-activated protein kinase, and antioxidant activity predicted for araloside C and stipuleanoside R2. Inhibition of transcription factor NF-κB had the greatest estimates for all four compounds with Pa – Pi = 0.99.

TABLE 2. Most Probable Antitumor Effects of *Oplopanax elatus* Phytocomponents

Compound	Antitumor effect	Pa – Pi
Araloside C	Lung cancer	0.83
Stipuleanoside R2	Lung cancer	0.82
Araloside C	Ovarian cancer	0.79
Stipuleanoside R2	Ovarian cancer	0.78
Araloside C	Melanoma	0.77
Stipuleanoside R2	Melanoma	0.76
Ginsenoside Rd	Lung cancer	0.74
Ginsenoside Re	Lung cancer	0.74
Araloside C	Breast cancer	0.72
Stipuleanoside R2	Breast cancer	0.71
Araloside C	Colorectal cancer	0.71

An analysis of literature on the biological activities of the studied compounds gave the following results.

Ginsenosides Rd and Re, araloside C, and stipuleanoside R2 possessed neuroprotective properties [32 – 36] and antitumor activity against glioblastoma, hepatocarcinoma, colorectal cancer, and breast cancer, including activation of apoptosis and suppression of angiogenesis [37 – 42]. They were also shown to have geroprotective activity [43] with suppressed development of atherosclerosis [44, 45] and diabetes [46]. Also, these compounds exhibited antioxidant, immunomodulating, antiviral, and antiallergic activity [47 – 53] and had positive effects on the cardiovascular system [54 – 56].

Besides, it should be emphasized that the properties identified for ginsenosides Rd and Re, araloside C, and stipuleanoside R2 from the analysis *in silico* and from the scientific literature were analogous to those observed in studies of the MPA, i.e., immunomodulating, including antiviral, antioxidant, neuroprotective, antistress, chemopreventive (against skin squamous cell carcinoma and hepatocarcinoma), and antitumor against ovarian and cervical adenocarcinoma, hepatocarcinoma, and kidney, lung, and stomach cancer. The MPA also suppressed increased IL-6 levels and activated apoptosis of tumor cells and TNF-α production [8 – 18, 57 – 68].

The above activities characteristic of ginsenosides Rd and Re, araloside C, and stipuleanoside R2 that were ana-

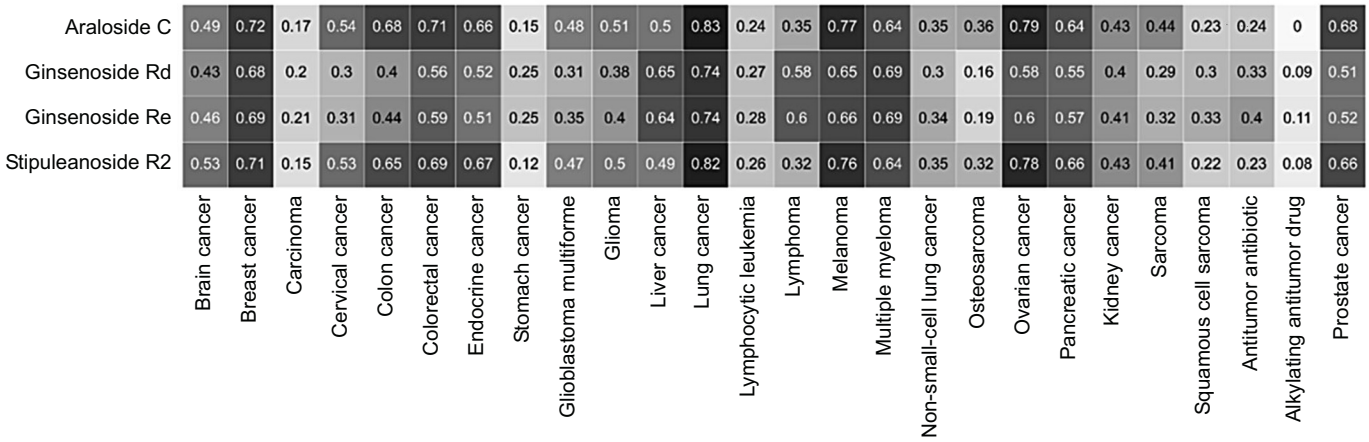


Fig. 3. Thermal map of Pa – Pi assessments calculated for antitumor effects and *Oplopanax elatus* Nakai compounds.

lyzed *in silico* and using literature data agreed fully with the concept of drugs intended for preventive oncology.

However, the analysis *in silico* and literature data demonstrated additional properties for ginsenosides Rd and Re, araloside C, and stipuleanoside R2 that were not previously studied for the MPA pharmacological composition. In particular, these compounds could be effective against glioblastoma, colorectal cancer, breast cancer, prostate cancer, pancreatic cancer, liver cancer, bladder cancer, and others, including suppression of tumor angiogenesis. They possessed cardioprotective and antiallergic activity and prevented development of atherosclerosis and diabetes. All these properties could be subjects of future research on the MPA pharmacological composition and could be considered for development of new complex adaptogens, i.e., geroprotectors for preventive oncology.

TABLE 3. Most Probable Mechanisms of Action Associated with Antitumor Effects

Mechanism	Associated antitumor effects	Pa – Pi values			
		Araloside C	Ginsenoside Rd	Ginsenoside Re	Stipuleanoside R2
AMP-activated protein kinase stimulator	Melanoma, multiple myeloma, pancreatic cancer, prostate cancer	0.89	0.88	0.88	0.87
Antioxidant	Melanoma, lung cancer, multiple myeloma, kidney cancer, prostate cancer	0.78	0.90	0.90	0.78
Apoptosis agonist	Melanoma, stomach cancer, breast cancer, lung cancer, bladder cancer, cervical cancer, colorectal cancer, multiple myeloma, pancreatic cancer, kidney cancer, liver cancer, osteosarcoma, lymphoma, prostate cancer, benign prostate hyperplasia	0.95	0.95	0.95	0.94
Caspase 3 stimulator	Prostate cancer, breast cancer, lung cancer, bladder cancer, kidney cancer, colorectal cancer, pancreatic cancer	0.74	0.85	0.85	0.74
Interleukin 2 agonist	Lymphoma	0.43	0.40	0.38	0.46
Interleukin 6 antagonist	Breast cancer, lung cancer, multiple myeloma	0.15	0.22	0.27	0.21
Topoisomerase I inhibitor	Prostate cancer, ovarian cancer, stomach cancer, breast cancer, lung cancer, colorectal cancer, multiple myeloma, pancreatic cancer, kidney cancer, liver cancer, squamous cell carcinoma, brain cancer	0.26	0.16	0.18	0.25
Transcription factor NF-κB inhibitor	Prostate cancer, stomach cancer, breast cancer, lung cancer, bladder cancer, colorectal cancer, multiple myeloma, kidney cancer, lymphoma, solid tumors	0.99	0.99	0.99	0.99
Tumor necrosis factor alpha release inhibitor	Prostate cancer, bladder cancer, multiple myeloma, liver cancer, lymphoma	0.61	0.66	0.65	0.60

CONCLUSION

Chromatograms and spectra obtained during the research could be used for standardization and quality control of the MPA.

Data obtained *in silico* and from the literature agreed with known characteristics of the biological activity of ginsenosides Rd and Re, araloside C, and stipuleanoside R2. The analysis *in silico* of the biological activity profiles identified the most probable mechanisms of antitumor activity of ginsenosides Rd and Re, araloside C, and stipuleanoside R2 and their possible additive/synergistic effects, including a broader spectrum of antitumor activity. Also, several pharmacological effects that were not previously known for the identified compounds were discovered. These data could become the basis for further research on ginsenosides Rd and Re, araloside C, and stipuleanoside R2 and extract from *O. elatus* rhizomes and roots.

Also, the research demonstrated the possibility for quality control and standardization of complex phytoadaptogens containing tetracyclic triterpene glycosides (ginsenosides Rd and Re) and pentacyclic triterpene glycosides derived from oleanolic acid (araloside C and stipuleanoside R2).

ACKNOWLEDGMENTS

The work was performed in the framework of the Basic Scientific Research Program in the Russian Federation for the long-term (2021 – 2030) (No. 122030100170-5) and with support in part by grants from the Commission on Biomedical Innovations and Technologies of the Ministry of Science and Higher Education of the Russian Federation.

REFERENCES

1. A. G. Panossian, T. Efferth, A. N. Shikov, et al., *Med. Res. Rev.*, **41**, 630 – 703 (2021); doi: 10.1002 / med.21743.
2. O. A. Bocharova, R. V. Karpova, E. V. Bocharov, et al., *Ross. Bioterapevticheskii Zh.*, **19**(2), 13 (2020).
3. O. A. Bocharova, R. V. Karpova, E. V. Bocharov, et al., *Ross. Bioterapevticheskii Zh.*, **19**(3), 12 (2020).
4. O. A. Bocharova, M. I. Davydov, A. Yu. Baryshnikov, et al., *Vestn. Ross. Akad. Med. Nauk*, No. 8 (21), (2009).
5. E. L. Al?perina, E. V. Bocharov, O. A. Bocharova, et al., *Critical Problems of Neuroimmunopathology* [in Russian], G. N. Kryzhanovskii, et al., (eds.), Genius Media, Moscow (2012).
6. A. Panossian, G. Wikman, and J. Sarris, *Phytomedicine*, **17**(7), 481 (2010).
7. A. N. Shikov, O. N. Pozharitskaya, V. G. Makarov, et al., *J. Ethnopharmacol.*, **154**(3), 481 (2014).
8. O. A. Bocharova, R. V. Karpova, E. V. Bocharov, et al., *Ross. Bioterapevticheskii Zh.*, **19**(4), 35 (2020).
9. O. Bocharova, R. Serebriakova, T. Philippova, et al., *Farm. Vestn. (Ljublana, Slov.)*, **48** (Spec. Iss.), 414 (2014).
10. O. A. Bocharova, M. M. Pozharitskaya, T. L. Chekalina, et al., *Bull. Exp. Biol. Med.*, **138**(6), 578 (2004).
11. E. V. Bocharov, V. G. Kucheryanu, G. N. Kryzhanovsky, et al., *Bull. Exp. Biol. Med.*, **141**(5), 560 (2006); E. V. Bocharov, V. G. Kucheryanu, G. N. Kryzhanovskii, et al., *Byull. Eksp. Biol. Med.*, **141**(5), 495 – 498 (2006).
12. O. A. Bocharova, M. I. Davydov, A. A. Klimenkov, et al., *Byull. Eksp. Biol. Med.*, **148**(7), 96 (2009).
13. O. A. Bocharova, M. A. Lyzhenkova, M. V. Mezentseva, et al., *Byull. Eksp. Biol. Med.*, **136**(12), 670 (2003).
14. N. P. Bochkov, O. A. Bocharova, A. A. Akseonv, et al., *Med. Genet.*, **4**(1), 15 (2005).
15. O. A. Bocharova, V. B. Matveev, R. V. Karpova, et al., *Bull. Exp. Biol. Med.*, **141**(5), 616 (2006); O. A. Bocharova, V. B. Matveev, R. V. Karpova, et al., *Byull. Eksp. Biol. Med.*, **141**(5), 555 – 558 (2006).
16. O. N. Kurennaya, R. V. Karpova, O. A. Bocharova, et al., *Russ. J. Genet.*, **49**(12), 1190 (2013); O. N. Kurennaya, R. V. Karpova, O. A. Bocharova, et al., *Genetika (Moscow)*, **49**(12), 1364 – 1369 (2013).
17. E. V. Bocharov, R. V. Karpova, I. V. Kazeev, et al., *Patol. Fiziol. Eksp. Ter.*, No. 3, 55 (2013).
18. R. V. Karpova, E. V. Bocharov, I. V. Kazeev, et al., *Patol. Fiziol. Eksp. Ter.*, No. 4, 51 (2013).
19. V. I. Sheichenko, O. A. Bocharova, O. P. Sheichenko, et al., *Zavod. Lab., Diagn. Mater.*, **72**(8), 15 (2006).
20. O. P. Sheichenko, O. A. Bocharova, V. I. Sheichenko, et al., *Vopr. Biol., Med. Farm. Khim.*, **5**(2), 20 (2007).
21. O. P. Sheichenko, O. A. Bocharova, B. A. Krapivkin, et al., *Vopr. Biol., Med. Farm. Khim.*, No. 10, 52 (2012).
22. I. V. Kazeev, O. A. Bocharova, V. E. Shevchenko, et al., *Teor. Osn. Khim. Tekhnol.*, **55**(6), 780 (2021).
23. I. V. Kazeev, O. A. Bocharova, V. E. Shevchenko, et al., *Teor. Osn. Khim. Tekhnol.*, **54**(6), 733 (2020).
24. O. A. Bocharova, I. V. Kazeev, V. E. Shevchenko, et al., *Khim.-farm. Zh.*, **56**(1), 32 – 38 (2022); *Pharm. Chem. J.*, **56**(1), 78 – 84 (2022).
25. O. A. Bocharova, V. E. Shevchenko, I. V. Kazeev, et al., *Khim.-farm. Zh.*, **56**(6), 29 – 37 (2022); *Pharm. Chem. J.*, **56**(6), 806 – 814 (2022).
26. O. A. Bocharova, I. V. Kazeev, N. S. Ionov, et al., *Cardiometry.*
27. A. G. Elenevskii, M. P. Solov'eva, and V. N. Tikhomirov, *Botany. Systematics of Higher or Terrestrial Plants* [in Russian], Akademiya, Moscow (2004).
28. D. A. Filimonov, D. S. Druzhilovskiy, A. A. Lagunin, et al., *Biomed. Chem.: Res. Methods*, **1**(1), e00004-e00004 (2018).
29. V. V. Poroikov, *Biochemistry (Moscow), Suppl. Ser. B: Biomed. Chem.*, **14**(3), 216 – 227 (2020); V. V. Poroikov, *Biomed. Khim.*, **66**(1), 30 – 41 (2020).
30. A. Dalby, J. G. Nourse, E. D. Hounshell, et al., *J. Chem. Inf. Comput. Sci.*, **32**(3), 244 – 255 (1992); doi: 10.1021/ ci00007a012.
31. A. A. Lagunin, R. K. Goel, D. Y. Gawande, et al., *Nat. Prod. Rep.*, **31**(11), 1585 – 1611 (2014).
32. Y. Y. Chen, Q. P. Liu, P. An, et al., *Phytomedicine*, **95**, Art. 153883 (2022); doi: 10.1016 / j.phymed.2021.153883.
33. X. Zhang, X. Liu, G. Hu, et al., NeuroReport, **31**(6), 466 – 472 (2020).
34. X. Zhang, Y. Wang, C. Ma, et al., *Am. J. Neurodegener. Dis.*, **5**(1), 52 – 61 (2016).
35. I. Madhi, J. H. Kim, J. E. Shin, et al., *Mol. Med. Rep.*, **24**(4), 698 (2021).
36. H. Wang, J. Lv, N. Jiang, et al., *Phytother. Res.*, Mar 29 (2021); doi: 10.1002 / ptr.6947.
37. G.-M. Liu, T.-C. Lu, M.-L. Sun, et al., *Biol. Pharm. Bull.*, **43**(10), 1534 – 1541 (2020); doi: 10.1248 / bpb.b20–00338.

38. X. Yang, M. Gao, M. Miao, et al., *J. Pharm. Pharmacol.*, **73**(2), 263 – 271 (2021); doi: 10.1093 / jpp / rgaa006.
39. E. Zhang, H. Shi, L. Yang, et al., *Oncol. Rep.*, **38**(1), 359 – 367 (2017); doi: 10.3892 / or.2017.5652.
40. Y. Nam, M. B. Wie, E. J. Shi, et al., *J. Appl. Toxicol.*, **35**(8), 927 – 944 (2015); doi: 10.1002 / jat.3093.
41. C. Liang, Y. Ding, H. T. Nguyen, et al., *Bioorg. Med. Chem. Lett.*, **20**(23), 7110 – 7115 (2010); doi: 10.1016 / j.bmcl.2010.09.074.
42. N. X. Nhiem, H. Y. Lim, P. V. Kiem, et al., *Bioorg. Med. Chem. Lett.*, **21**(20), 6143 – 6147 (2011); doi: 10.1016 / j.bmcl.2011.08.024.
43. T. Yokozawa, A. Satoh, and E. J. Cho, *J. Pharm. Pharmacol.*, **56**(1), 107 – 113 (2004); doi: 10.1211 / 0022357022449.
44. J. Li, Z.-Z. Xie, Y.-B. Tang, et al., *Eur. J. Pharmacol.*, **652**(1 – 3), 104 – 110 (2011); doi: 10.1016 / j.ejphar.2010.11.017.
45. Y. Luo, S. Lu, Y. Gao, et al., Aging (N. Y.), **12**(2), 1704 – 1724 (2020); doi: 10.18632 / aging.102708.
46. H. Wang, Y. Teng, S. Li, et al., *Molecules*, **26**(21), 6657 (2021); doi: 10.3390 / molecules26216657.
47. R. Ye, J. Han, X. Kong, et al., *Biol. Pharm. Bull.*, **31**(10), 1923 – 1927 (2008); doi: 10.1248 / bpb.31.1923.
48. X.-Y. Gao, G.-C. Liu, J.-X. Zhang, et al., *Front. Pharmacol.*, **13**, 754191 (2022); doi: 10.3389 / fphar.2022.754191.
49. G. H. Lee, W. J. Lee, J. Hur, et al., *Molecules*, **25**(1), 188 (2020); doi: 10.3390 / molecules25010188.
50. X. Su, Z. Pei, and S. Hu, *Int. Immunopharmacol.*, **20**(2), 283 – 289 (2014); doi: 10.1016 / j.intimp. 2014.03.008.
51. M. Wang, R. Wang, X. Xie, et al., *Biomed. Pharmacother.*, **117**, 109143 (2019); doi: 10.1016 / j.biopha.2019.109143.
52. Y. Ding, Q. Zhao, and L. Wang, *Chem.-Biol. Interact.*, **306**, 131 – 137 (2019); doi: 10.1016 / j.cbi.2019.04.025.
53. H. He, X. Li, H. Yu, et al., *J. Nat. Med.*, **73**(2), 339 – 352 (2019); doi: 10.1007 / s11418-018-1256-0.
54. H. Sun, S. Ling, D. Zhao, et al., *Front. Pharmacol.*, **11**, 532041 (2020); doi: 10.3389 / fphar.2020.532041.
55. M. Wang, R. Wang, X. Xie, G. Sun, et al., *Biomed. Pharmacother.*, **117**, 109143 (2019); doi: 10.1016 / j.biopha.2019.109143.
56. J. Wang, X. Li, G. Peng, et al., *Evidence-Based Complementary Altern. Med.*, **2022**, 2056630 (2022); doi: 10.1155 / 2022 / 2056630.
57. O. A. Bocharova, R. V. Karpova, V. A. Golubeva, et al., *Byull. Eksp. Biol. Med.*, **128**(10), 403 – 407 (1999).
58. O. A. Bocharova, A. Yu. Baryshnikov, and M. I. Davydov, *Phytoadaptogens in Oncology and Gerontology* [in Russian], MIA, Moscow (2008).
59. O. A. Bocharova, R. V. Karpova, V. B. Matveev, et al., *Ross. Bioterapevticheskii Zh.*, **3**(1), 90 – 95 (2004).
60. E. V. Bocharov, I. A. Ivanova-Smolenskaya, V. V. Poleshchuk, et al., *Byull. Eksp. Biol. Med.*, **149**(6), 619 – 621 (2010).
61. E. V. Bocharov, O. A. Bocharova, Yu. N. Solov'ev, et al., *Byull. Eksp. Biol. Med.*, **161**(5), 674 – 677 (2016).
62. E. V. Bocharov, O. A. Bocharova, R. V. Karpova, et al., *Ross. Bioterapevticheskii Zh.*, **17**(2), 69 – 78 (2018).
63. O. A. Bocharova, A. V. Revishchin, E. V. Bocharov, et al., *Lab. Zhivotn. Nauchn. Issled.*, No. 2, 47 – 53 (2021).
64. O. A. Bocharova, E. V. Bocharov, V. G. Kucheryanu, et al., *Ross. Bioterapevticheskii Zh.*, **18**(4), 25 – 33 (2019).
65. O. A. Bocharova, E. V. Bocharov, R. V. Karpova, et al., *Byull. Eksp. Biol. Med.*, **157**(2), 223 – 226 (2014).
66. E. V. Bocharov, R. V. Karpova, A. A. Vershinskaya, et al., *Ross. Bioterapevticheskii Zh.*, **14**(2), 85 – 90 (2015).
67. O. A. Bocharova and A. Yu. Baryshnikov, *Phytoadaptogens in Oncology* [in Russian], ZooMedVet, Moscow (2004).
68. M. M. Pozharitskaya, O. A. Bocharova, T. L. Chekalina, et al., *Modern Aspects of Pathogenesis and Treatment of Leukoplakia of Oral Cavity Mucous Membrane* [in Russian], Moscow (2004).