https://doi.org/10.31925/farmacia.2020.5.7 **ORIGINAL ARTICLE**

STUDY AND MODELING OF EXTRACTION PROPERTIES OF FLUOROORGANIC SOLVENTS IN REGARD TO LOW-POLAR BIOLOGICALLY ACTIVE SUBSTANCES FROM PLANT RAW MATERIALS

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Abstract

The goal of this work was the studying and modelling of the extraction properties of fluoroorganic solvents in regard to low-polar biologically active substances (BAS) from plant raw materials (PRM). *Anethum graveolens* L., *Foeniculum vulgare* Mill., *Pastinaca sativa* L., *Pimpinella anisum* L., *Silybum marianum* L. fruits, *Curcuma longa* L. roots, *Eucalyptus viminalis* Labill., *Laurus nobilis* L. leaves, *Hypericum perforatum* L. herbs, and *Syzygium aromaticum* L. buds were used. As solvents, we used Novec 1230, Novec 7100, MR6S4, and R141b. Quantitative and qualitative analyses of BAS were carried out by RP HPLC and GC-MS. We also used a circulating method in Soxhlet apparatus. A mathematical model that quantitatively describes the extraction properties of fluoroorganic solvents using molecular descriptors such as the relative fraction of fluorine atoms in the molecule of the fluoroorganic solvent and *LTPSA* has been developed.

Rezumat

În acest studiu au fost evaluate proprietățile extractive ale solvenților fluoroorganici, ținând cont de polaritatea substanțelor (BAS) din materiile prime vegetale (PRM). Au fost utilizate fructele de *Anethum graveolens* L., *Foeniculum vulgare* Mill., *Pastinaca sativa* L., *Pimpinella anisum* L., *Silybum marianum* L., rădăcinile de *Curcuma longa* L., frunzele de *Eucalyptus viminalis* Labill., *Laurus nobilis* L., partea aeriană de *Hypericum perforatum* L. și mugurii de *Syzygium aromaticum* L.. Solvenții folosiți au fost Novec 1230, Novec 7100, MR6S4 și R141b. Analizele cantitative și calitative ale BAS au fost efectuate folosind ca metode RP-HPLC și GC-MS. S-a dezvoltat un model matematic care descrie cantitativ proprietățile de extracție ale solvenților fluoroorganici cu descriptori moleculari.

Keywords: fluoroorganic solvents, extraction properties, mathematical model

Introduction

Currently, separation of low-polar biologically active substances (BAS) from plant raw materials with the use of liquefied gases and supercritical fluids are considered to be the most promising technologies in the world [1-5].

It is conditioned by the fact that these technologies have a number of advantages: high yield of low-polar BAS (90% - 98%), sparing extraction conditions, environmental, fire, and explosion safety, low toxicity to humans.

However, these technologies also have a number of significant drawbacks: the need to use special equipment that has to operate under excessive pressure (2 - 350 bar), the need to use a refrigeration unit for vapour condensation, additional energy costs for the operation of the refrigeration unit, low selectivity of extraction of fatty oils and essential oils between each other, etc.

It should be noted that only in the supercritical state (at elevated temperature and high pressure), carbon dioxide allows selective separation of essential oils from vegetable raw materials in their joint presence with triglycerides [6].

Therefore, it is urgent to search for new solutions in the technology of selective isolation of low-polar BAS from PRM, which allow avoiding the above disadvantages.

One of such innovative solutions can be the use of fluoroorganic solvents owing to their unique physical and chemical properties driven by the presence of fluorine atoms in the carbon skeleton of the molecule, which gives them weak intermolecular forces and causes these substances to have low boiling points, evaporation heat, heat capacity, surface tension, toxicity, and also gives them hydrophobic and even lipophobic properties [7].

The analysis of the literature revealed that at the moment, fluoroorganic solvents of a new generation have appeared on an industrial scale in Russia; they have the advantages in a number of parameters in comparison to liquefied gases and supercritical fluids.

Some fundamental parameters of fluoroorganic solvents and liquefied gases (from the technological point view) are presented in Table I [8-13].

Table I

Some fundamental parameters of fluoroorganic solvents and liquefied gases

Parameter	Type of fluoroorganic solvent and liquefied gas							
	Novec 1230	Novec 7100	MR6S4	R141b	R22	R227ea	RC318	R744
1. Empirical formula	$C_6F_{12}O$	$C_4F_9OCH_3$	$C_4H_3OF_7$	$C_2H_3Cl_2F$	$CHClF_2$	C_3F_7H	C_4F_8	CO_2
2. Molecular weight, g/mol	316	250	200	117	67	170	200	44
3. Pressure 20 °C, MPa	0.040	0.027	0.020	0.081	0.91	0.391	0.272	6.0
4. Boiling point, °C	49	61	59	32	-41	-16	-6	-79
5. Heat of vaporization, kJ/L	141	169	214	257	278	181	178	144
6. Density 20 °C, kg/m³	1,600	1,510	1,520	1,240	1,200	1,407	1,517	930
7. Dielectric constant	1.8 - 2.3	7.4	n/a	8.1	3.1	2.0	1.0	1.6
7. Global warming potential (GWP)	1	320	204 - 575	630 - 782	1,760	3,300	10,300	1
8. Ozone depletion potential (ODP)	0	0	0.02	0.12	0.055	0	0	0
9.Toxicity, ppm	4,000	750	4	500	1,000	1,000	1,000	5,000
10. Approx. price as to 08/2019, US dollars *per* kg	40 ± 4	95 ± 9	405	13 ± 2	12 ± 2	22 ± 2	40 ± 5	0.15

As can be seen from the data in Table I, fluoroorganic solvents in many physical, chemical, environmental, and toxicological parameters do not differ very much from freons, but are inferior to carbon dioxide. At the same time, their price is slightly higher than that of freons and much higher than of carbon dioxide, which is one of the limiting factors of their widespread use in industry.

However, owing to their unique properties, these solvents are increasingly being used in various sectors of the economy as solvents, heat-conducting liquids, and fire extinguishing agents [14-15].

As a result of the patent search, we have found only a few patents in the EU and the US, regarding the methods for extraction of fatty and essential oils from vegetable raw materials using fluoroorganic solvents or their mixture with other solvents [16-18].

These results show the availability of limited information on the extraction properties of fluoroorganic solvents for use in the pharmaceutical industry, as well as high prospects for research in this field.

Taking into account the above material, we have conducted systematic studies on the extraction properties of fluoroorganic solvents with respect to various low-polar BAS, and on their basis, an attempt is made to explain theoretically and describe quantitatively the experimental data obtained.

The goal of this work was the studying and modelling of the extraction properties of fluoroorganic solvents in regard to low-polar biologically active substances (BAS) from plant raw materials (PRM).

Materials and Methods

Plant raw materials

Ground plant raw materials with a particle size of 0.1 - 0.5 mm were used for research: *Anethum graveolens* L. fruits, LLC Pharmaceutical shop “Medicinal plants”, Kharkiv, Ukraine, batch no. 981117, bbd 09/2020. *Curcuma longa* L. roots, “Goldiee”, Nayaganj, Kanpur, India, batch no. 827, bbd 01/2020. *Foeniculum vulgare* Mill. fruits, LLC Pharmaceutical shop “Medicinal plants”, Kharkiv, Ukraine, batch no. 135117, bbd 08/2020. *Eucalyptus viminalis* Labill. leaves, “Krasnogorskleksredstva” company, Krasnogorsk, Russia, batch no. 100917, bbd 10/2020. *Hypericum perforatum* L. herbs, LLC Pharmaceutical shop “Medicinal plants”, Kharkiv, Ukraine, batch no. 120717, bbd 07/2019. *Laurus nobilis* L. leaves, LLC “Standart”, Krasnodar, Russia, batch no. 02042019, bbd 04/2020. *Pastinaca sativa* L. fruits (Globular cultivar), “Pnsemena” company, Ukraine, batch no. 454124, bbd 12/2021. *Pimpinella anisum* L. fruits, LLC Pharmaceutical shop “Medicinal plants”, Kharkiv, Ukraine, batch no. 135117, bbd 08/2020. *Silybum marianum* L. fruits, “Biocor” company, Penza, Russia, batch no. 040919, bbd 09/2021. *Syzygium aromaticum* L. buds, “Lechec” firm, Kharkiv, Ukraine, batch no. 082018, bbd 08/2020.

Chemicals

Carvone (CAS 6485-4D-1); eugenol (CAS 97-53-0); trans-anethole (CAS 4180-23-8), xanthotoxin (CAS 298-81-7) were from Sigma-Aldrich, Merck, with content ≥ 98.0%; evcalimin standard sample of the All Russian Scientific Research Institute of Medicinal and Aromatic Plants (a sum of macrocarpales); spissum extract of Chlorophyllipt of the State Pharmacopoeia of Ukraine (a sum of cupric chlorophylls, euglobals with monoterpenoid structure and macrocarpales), were used as reference substances.

Fluoroorganic solvents

Novec 1230 and Novec 7100 were from the USA, 3M Company; MR6S4 was from Great Britain, Aesica Queenborough Ltd; R141b DGX was from France, Arkema Inc., with content ≥ 99.0%.

Reverse phase high performance liquid chromatography (RP HPLC)

Analysis of biologically active substances was carried out using the method of RP HPLC on Agilent Technologies device, series Agilent 1200 Infinity, USA. The process of analysis was carried out under the following conditions: 1% aqueous solution of formic acid was used as mobile phase (A), and ethanol 96% vol. was used as mobile phase (B), with a linear gradient elution mode; mobile phase velocity was 0.5 mL/min; chromatographic column: Supelco Ascentis express C18, length 100 mm, internal diameter 4.6 mm, particle size 2.7 µm; chromatographic column temperature: 35°C; sample volume: 1 µL. The conditions for RP HPLC analysis were the same as in the work by Zhilyakova *et al.* [19]. Analytical wavelengths: 240 nm (carvone), 275 nm (euglobals and macrocarpales), 280 nm (eugenol), 284 nm (anethole) and 302 nm (xanthotoxin).

GC-MS method of analysis

Qualitative analysis of extracts was carried out by GC-MS method using equipment GCMS-QP2010 Ultra with a mass analyser, by Shimadzu, Japan. Column: Zebron ZB-5MS, length 30 m, inside diameter 0.25 mm, film thickness 0.25 µm; liquid phase: 5% – polysilarylene and 95% – polydimethylsiloxane; temperature settings: from 70°C to 325/350°C. Gas-carrier: helium with a stable flow of 3.0 mL/min. Detection regime: total ion current (SCAN) in the range m/z from 30 to 500 Da with scanning velocity 1,000 and result time 0.5 sec. The injection volume was 1 µL.

Method of extraction

A sample of ground plant raw material weighing 5.00 g (particle size 0.1 - 0.5 mm) was placed in the Soxhlet extractor; the raw material was poured with 25.0 mL of the extractant and extracted for a specified period. The resulting solution was evaporated until an extract was obtained, and the latter was blown with airflow for 5 - 10 minutes. The extract was dissolved in ethanol 96% vol. The solution was weighed, its density was determined, and it was analysed for the content of biologically active substances using the method of RP HPLC.

Theoretical part

To construct a mathematical model that quantitatively describes the extraction properties of fluoroorganic solvents, the authors used two working hypotheses based on the laws of physical and colloidal chemistry and two molecular descriptors [20, 21].

Working hypothesis 1: the extraction properties of fluoroorganic solvents should be associated with a change of chemical potential in the extraction system, which is represented by two types of Gibbs energies: surface energy (ΔG_1) and interaction energy of BAS molecules with solvent molecules (ΔG_2).

Working hypothesis 2: surface energy (ΔG_1) is directly proportional to the limit value TPSA of BAS molecule for fluoroorganic solvent (*LTPSA*), and interaction energy of BAS molecules with solvent molecules (ΔG_2) is directly proportional to the product of surface energy and the exponent of the relative fraction of fluorine atoms in the molecule of fluoroorganic solvent (1-φ_F).

These working hypotheses are presented below in equations (1) - (4):

$$RT \cdot \ln\left(\frac{N_0 - N}{N}\right) = \Delta\mu \quad (1)$$

$$\Delta\mu = \Delta G_1 + \Delta G_2 \quad (2)$$

where R is gas constant, 8.314, J/(mol·K);

T is absolute temperature, K;

N_0 is the total amount of BAS in the extraction system, mol;

N is the amount of BAS in the solvent, mol;

$\Delta\mu$ is change of chemical potential, J;

ΔG_1 is a change in Gibbs energy (J) due to changes in surface energy, which is associated with molecular descriptor LTPSA, equation (3):

$$\Delta G_1 = \sigma \cdot LTPSA \quad (3)$$

where σ is solvent surface tension, N/m²;

LTPSA is the experimental value of the limit value of the molecular descriptor TPSA for molecules of low-polar BAS extracted by solvent, Å²;

ΔG_2 is a change of Gibbs energy (J) due to energy of interaction of BAS molecules with solvent molecules, expressed in terms of surface energy and parameter (1-φ_F), in the form of equation (4):

$$\Delta G_2 = \sigma \cdot LTPSA \cdot \exp[k \cdot (1 - \varphi_F + b)] \quad (4)$$

where φ_F is the relative fraction of fluorine atoms in the solvent molecule;

k and b are empirical constants.

In the case of the adequacy of equations (2) - (4), as well as under the additional condition that $\Delta\mu = \sigma \cdot A$ = const, the experimental data should be well approximated by sigma function having the following form (5):

$$LTPSA = \frac{A}{1 + \exp[k \cdot (1 - \varphi_F + b)]} \quad (5)$$

Parameter (φ_F) was calculated by equation (6):

$$\varphi_F = \frac{n_F}{\sum n_i}, \qquad (6)$$

where n_F is the number of fluorine atoms in the solvent molecule, units;
n_i is the number of i-atoms in the solvent molecule, units.
A molecular TPSA descriptor for BAS was found in PubChem Database [13].
Calculation method
Regression analysis was used to determine the degree of consistency between the theoretically developed mathematical model (5) and the experimentally obtained data. At the same time, the values of constants and their errors were found using Origin 6.1 program.

Results and Discussion

In the first part of the research, systematic studies of the extraction properties of fluoroorganic solvents Novec 1230, Novec 7100, MR6S4, and R141b were carried out with respect to various types of low-polar BAS from plant raw materials (mainly from essential oils), the materials of which are partially presented in such works as [22-24].
In this case, the extraction of BAS from plant raw materials was carried out using the circulation method in Soxhlet apparatus for three hours. The results of the studies are presented in Table II.

Table II
Results of systematic studies on the extraction properties of fluoroorganic solvents

Type of PRM	Type of BAS	Yield of BAS, %*	Type of solvent	Note
1. *Anethum graveolens* L. fruits	Carvone	97 ± 4	Novec 1230	Limonene was detected. Triglycerides were undetected
		95 ± 4	Novec 7100	Limonene and triglycerides were detected
2. *Curcuma longa* L. roots	Sum of curcuminoids	None	Novec 1230	Curcumene, zingiberene, Ar-tumerone and curlone were detected
		None	Novec 7100	
		17 ± 1	MR6S4	
		16 ± 1	R141b	
3. *Foeniculum vulgare* Mill. fruits	Anethole	94 ± 4	Novec 1230	Fenchone was detected. Triglycerides were undetected
		83 ± 4	Novec 7100	Fenchone and triglycerides were detected
4. *Eucalyptus viminalis* Labill. leaves	Euglobals of mono-terpenoid structure	None	Novec 1230	1,8-cineole was detected. Chlorophylls and macrocarpales were undetected
		54 ± 3	Novec 7100	
	Euglobals of mono-terpenoid structure	48 ± 3	MR6S4	1,8-cineole and chlorophylls were detected
	Macrocarpales	44 ± 2		
	Euglobals mono-terpenoid structure	99 ± 4	R141b	
	Macrocarpales	51 ± 3		
5. *Hypericum perforatum* L. herbs	Hyperforin	None	Novec 1230	-
		99 ± 4	Novec 7100	Adhyperforin was detected. Chlorophylls were undetected
6. *Laurus nobilis* L. leaves	Eugenol	99 ± 3	Novec 1230	Costunolide, methyl eugenol, 1,8-cineole were detected
		99 ± 3	Novec 7100	
		99 ± 4	R141b	Costunolide, methyl eugenol, 1,8-cineole, chlorophylls were detected
7. *Pastinaca sativa* L. fruits	Xanthotoxin	None	Novec 1230	Octyl butyrate was detected. Triglycerides were undetected
		72 ± 4	Novec 7100	Xanthotoxol, bergapten, octyl butyrate and triglycerides were detected
		75 ± 4	MR6S4	
		66 ± 3	R141b	
8. *Pimpinella anisum* L. fruits	Anethole	99 ± 4	Novec 1230	Triglycerides were undetected
		94 ± 3	Novec 7100	Triglycerides were detected
9. *Silybum marianum* L. fruits	Triglycerides	None	Novec 1230	-
		≤ 10	Novec 7100	
		99 ± 4	MR6S4	
		99 ± 4	R141b	
10. *Syzygium aromaticum* L. buds	Eugenol	48 ± 3	Novec 1230	Caryophyllene, humulene, eugenyl acetate were detected
		86 ± 5	Novec 7100	

* The mean value and its confidence interval (Mean ± SEM) are calculated with repeat counts n = 3 and significance level p = 0.05.
Conditions: extraction method: circulating in Soxhlet apparatus, extraction time: three hours, the ratio of PRM to solvent 1:5 (w/v).

As can be seen from the results of Table II, the yield for most of the studied low-polar BAS (anethole, carvone, eugenol, hyperforin, and triglycerides) for three hours of extraction reaches 83 - 100%, 66 - 75% for xanthotoxin, 44 - 53% for euglobals, and 16 - 17% for the sum of curcuminoids. The obtained results were the basis for a number of patents of the Russian Federation for new methods for obtaining essential oils and extracts enriched with target low-polar BAS (furanocoumarins, monoterpene series euglobals, hyperforin, etc.) [25-31]. These results show that the technology of use of fluoroorganic solvents is comparable with those for separation of low-polar BAS from PRM using liquefied gases and supercritical fluids in terms of fire, explosion, and environmental safety, low toxicity and yield of BAS, but surpasses them in its selectivity, simplicity of organization, and conditions of the extraction process [1, 32, 33].

In the second part of the research, the analysis of the obtained data was carried out for the possibility of their mathematical formalization, construction of a mathematical model and prediction of the extraction properties of fluoroorganic solvents.

For this purpose, the authors used the following molecular descriptors: relative fraction of fluorine atoms in the solvent molecule (φ_F) and topological polar surface area of the low-polar BAS molecule (TPSA). The results obtained are presented in Table III.

Table III

The extraction properties of fluoroorganic solvents and molecular descriptors of low-polar BAS and solvents

Type of BAS	Type of fluoroorganic solvent					
	TPSA, Å²	Novec 1230	Novec 7100	MR6S4	R12/ R22 [1]	R141b
1. Caryophyllene, curcumene, humulene, limonene, zingiberene	0	Y*	Y	Y	n/a**	Y
2. Anethole, 1,8-cineole	9	Y	Y	n/a	Y	n/a
3. Carvone	17	Y	Y	n/a	Y	n/a
4. Ar-tumerone, curlone		Y	Y	Y	n/a	Y
5. Fenchone		Y	Y	n/a	n/a	n/a
6. Methyleugenol	19	Y	Y	n/a	n/a	Y
7. Heptyl butyrate	26	Y	Y	Y	Y	Y
8. Costunolide		Y	Y	n/a	n/a	Y
9. Eugenol	29	Y	Y	n/a	n/a	n/a
10. Acetyl eugenol	36	P	Y	Y	n/a	Y
11. Xanthotoxin, bergapten	49	N	Y	Y	Y	Y
12. Xanthotoxol	60	N	Y	Y	Y	Y
13. Adhyperforin, hyperforin	71	N	Y	n/a	n/a	n/a
14. Triglycerides	79	N	P	Y	Y	Y
15. Euglobal IIb	84	N	P	Y	n/a	Y
16. Macrocarpal C	95	N	N	P	n/a	Y
17. Chlorophyll *a*	96	N	N	P	Y	Y
18. Macrocarpal A	115	N	N	N	n/a	Y
19. Limiting value of TPSA of low-polar BAS molecules for the solvent (*LTPSA*)		30 ± 5	85 ± 5	95 ± 5	110 ± 5	115 ± 5
20. Relative proportion of fluorine atoms in solvent's molecule (φ_F)		0.63	0.50	0.47	0.40	0.13

* Y means that BAS is extracted by the solvent during 3 h (yield ≥ 50%); N means that BAS is not extracted by the solvent during 3 h (yield ≤ 10%); P means that BAS is poorly extracted by the solvent during 3 h (10% ≤ yield ≤ 50%); ** n/a means that data is not available.

Qualitative data on the possibility/impossibility of extraction of low-polar BAS, fluoroorganic solvent (lines 1 - 18) presented in Table III, allow to formalize and find the limit value of the molecular descriptor *LTPSA* of low-polar BAS for solvents (line 19) and associate it with the second molecular descriptor, the relative fraction of fluorine atoms in the solvent molecule (φ_F) (line 20).

In the third part of the studies, the experimentally obtained data were compared as for *LTPSA* and φ_F (lines 19, 20 in Table III) and the developed mathematical model (equation (5)) using regression analysis.

Figure 1 presents the experimental points and parameters of the regression line, which is constructed according to equation (5) in Origin 6.1 program.

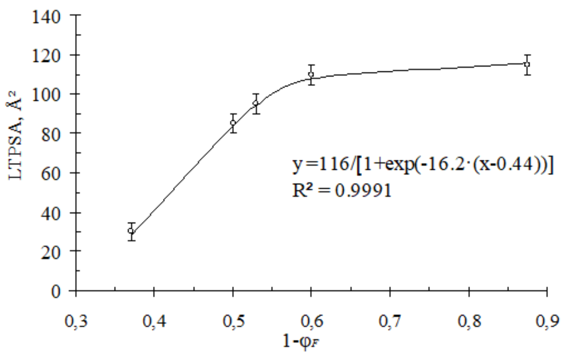

Figure 1.

The experimental data and parameters of the regression line

From Figure 1 it is seen that the experimental data are in good agreement with the theoretically developed mathematical model in the form of equation (5) (empirical constants are A = 116.0 ± 1.3, k = -16.2 ± 0.6, b = 0.44 ± 0.01, and the coefficient of determination is $R^2 \geq 0.99$), which gives grounds for adoption of working hypotheses that have been suggested to explain the extraction properties of fluoroorganic solvents.

It should be noted that constant (*A*) in equation (5) can be interpreted as the maximum value of *LTPSA* molecular descriptor for low-polar BAS molecules, above which BAS molecules will not pass into the fluoroorganic solvent even with a minimum content of fluorine atoms. This is explained by the emergence of significant repulsive forces between the polar part of BAS molecules and solvent molecules.

In general, resulting equation (5) allows: (1) theoretical calculation of *LTPSA* value of BAS molecules that can be extracted with the fluoroorganic solvent with a given relative fraction of fluorine atoms in its molecule; (2) theoretical selection of the fluoroorganic solvent with the desired value of the parameter of relative fraction of fluorine atoms in its molecule for selective extraction of target low-polar BAS from PRM by their TPSA, and this parameter must meet the condition TPSA < *LTPSA*.

Thus, for the first time, the authors systematically studied the extraction properties of various fluoroorganic solvents with respect to low-polar BAS with a circulating extraction method in Soxhlet apparatus.

The obtained data showed comparable results in environmental safety, toxicity, extraction time, and yield of BAS with the technology of liquefied gases and supercritical fluids, but at the same time demonstrate advantages in selectivity, simplicity of organization and conditions of the extraction process.

The use of these types of solvents is suitable for selective extraction of low-polar BAS; at the same time, the development of a new direction in the technology of integrated processing of PRM, which meets the basic principles of "green chemistry", is rather promising.

A mathematical model that allows predicting the possibility or impossibility of extraction of low-polar BAS molecules by the fluoroorganic solvent or, on the contrary, helps to choose the necessary type of the fluoroorganic solvent for extraction of a certain type of BAS has been suggested.

Conclusions

It has been found that the yield of low-polar BAS from PRM depends on the value of the polar part in the BAS molecule and the relative proportion of fluorine atoms in the fluoroorganic solvent molecule. A mathematical model that quantitatively describes the extraction properties of fluoroorganic solvents using molecular descriptors such as the relative fraction of fluorine atoms in the molecule of the fluoroorganic solvent and *LTPSA* has been developed. The developed mathematical model allows theoretical prediction and selection of the optimal type of the fluoroorganic solvent for selective extraction of target low-polar BAS from PRM. The obtained practical results showed advantages in selectivity, simplicity of organization, and conditions of the extraction process using fluoroorganic solvents in comparison with the technologies of liquefied gases and supercritical fluids, which is confirmed by a number of patents of the Russian Federation. Conducted systematic studies on extraction properties of various types of fluoroorganic solvents in regards to low-polar BAS from PRM, significantly expand our knowledge in the field of phytotechnology and can be used in the future for the development of new methods for isolation of different types of low-polar BAS on their basis.

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Conflict of interest

The authors declare no conflict of interest.

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