Research of *Dracocephalum palmatum* S. and *Dracocephalum ruyschiana* L. originating from Yakutia and identification of metabolites by tandem mass spectrometry

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Abstract. *Dracocephalum palmatum* Stephan and *Dracocephalum ruyschiana* L. contains a large number of target analytes, which are biologically active compounds. High performance liquid chromatography (HPLC) in combination with a BRUKER DALTONIKS ion trap (tandem mass spectrometry) was used to identify target analytes in extracts of *D. palmatum* Stephan and *D. ruyschiana* L., originating from Yakutia. The results of initial studies revealed the presence of 61 compounds, of which 53 were identified for the first time in genus *Dracocephalu*m. These are flavones: Apigenin 8-*C*-pentoside-6-*C*-hexoside, Apigenin 7-sulfate; Chrysin 6-*C*-glucoside, Chrysin glucuronide; flavanols: Kaempferol, Dihydrokaempferol, Astragalin; flavan-3-ol (epi)Catechin, phenolic acids: Methylgallic acid; Hydroxy methoxy dimethylbenzoic acid; Ellagic acid; Caffeoylshikimic acid; Prolithospermic acid; 3,4-*O*-dicaffeoylquinic acid; salvianolic acid G; stilbenes pinosylvin and resveratrol; anthocyanins Petunidin, Pelargonidin-3-*O*-glucoside; Peonidin-3-*O*-glucoside; Cyanidin 3-(acetyl)hexose; perillic acid; lignans: Hinokinin, Dimethyl-secoisolariciresinol, Podophyllotoxin, carotenoids: Apocarotenal, 5,8-epoxy-alpha-carotene; etc.

1 Introduction

Yakutia is a subject of the Russian Federation, which is one of the largest subnational subjects. Yakutia is located in several climatic zones and on its territory, there is an amazing variety of plant resources, including medicinal plants. One of these medicinal plants are plants belonging to the genus *Dracocephalum. Dracocephalum palmatum*

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Stephan and *Dracocephalum ruyschiana* L. (Section Buguldea Benth., Subgenus *Eudracocephalum* Briq., Genus *Dracocephalum* L., Family *Lamiaceae*), are a perennial rhizomatous plant with numerous stems and ovate-rounded, pinnatifid leaves, and purple flowers on short stalks gathered in false whorls at the end of the stems in an oblong inflorescence (Fig. 1).

Several plants belonging to the genus *Dracocephalum* have been reported to possess anticancer, antioxidant, and cardio-protective effects [32]. Lee et al. (2020) reported about the anticancer activity of *D. palmatum* Stephan, dried leaves of *D. palmatum* and the effects of various extracts on intracellular reactive oxygen species (ROS) levels, cell cycle distribution, apoptotic cell population and apoptosis-related protein levels were extensively studied to assess potential anti-cancer activity. Research by Kim et al. (2020) was aimed at evaluating the tumor suppressive effect of *D. palmatum* extract in diffuse large cell lymphoma and the underlying mechanism. Fractionation of *D. palmatum* extract by thin layer chromatography and analysis of the fraction with biologically active compounds based on liquid chromatography/mass spectrometry demonstrated that flavonoids may be responsible for most, if not all, of the anti-lymphoma effect. Extensive research is currently underway to identify bioactive flavonoids from *D. palmatum* extracts.

A B

Fig. 1. A: *Dracocephalum palmatum* S. B: *Dracocephalum ruyschiana* L.

This research examines a detailed metabolomic and comparative analysis of leaves and twigs of *D. palmatum* Stephan and *D. ruyschiana* L., originated from Yakutia and collected by scientists of North-Eastern Federal University.

2 Methods

2.1 Materials

As an object of research, we used leaves and twigs of *D. palmatum* Stephan and *D. ruyschiana* L., originated from Yakutia. All samples were morphologically authenticated according to the current standard of Russian Pharmacopoeia [29].

2.2 Chemicals and Reagents

HPLC-grade acetonitrile was purchased from Fisher Scientific (Southborough, UK), MS-grade formic acid was from Sigma-Aldrich (Steinheim, Germany). Ultra-pure water was

prepared from a SIEMENS ULTRA clear (SIEMENS water technologies, Germany), and all other chemicals were analytical grade.

2.3 Fractional maceration

To obtain highly concentrated extracts, fractional maceration was applied. In this case, the total amount of the extractant (methyl alcohol of reagent grade) is divided into 3 parts and is consistently infused on *Dracocephalum* with the first part, then with the second and third. The infusion time of each part of the extractant was 7 days.

2.4 Liquid chromatography

HPLC was performed using Shimadzu LC-20 Prominence HPLC (Shimadzu, Japan) was used, equipped with an UV-sensor and a Shodex ODP-40 4E reverse phase column to perform the separation of multicomponent mixtures. The gradient elution program was as follows: 0.01-5 min, 100% CH_3CN; 5-45 min, 100-25% CH_3CN; 45-55 min, 25-0% CH_3CN; control washing 55-60 min 0% CH_3CN. The entire HPLC analysis was done with a ESI detector at wavelengths of 230 ηm and 330 ηm; the temperature corresponded to 17°C. The injection volume was 1 ml.

2.5 Mass spectrometry

MS analysis was performed on an ion trap amaZon SL (BRUKER DALTONIKS, Germany) equipped with an ESI source in negative ion mode. The optimized parameters were obtained as follows: ionization source temperature: 70 ° C, gas flow: 4 l/min, nebulizer gas (atomizer): 7.3 psi, capillary voltage: 4500 V, end plate bend voltage: 1500V, fragmentary: 280 V, collision energy: 60 eV. A four-stage ion separation mode (MS/MS mode) was implemented.

3 Results

Six of the most consumed extracts of *D. palmatum* Stephan and *D. ruyschiana* L. were analyzed by HPLS-MS/MS ion trap to better interpret the diversity of available phytochemicals. All of them have a rich bioactive composition. The structural identification of each compound was carried out on the basis of their accurate mass and MS/MS fragmentation by HPLC-ESI-ion trap-MS/MS. Sixty-one biologically active compound was successfully identified characterized by comparing fragmentation pattern and retention time. Other compounds were identified by comparing their MS/MS data with available literature. All the identified compounds along with molecular formulas, m/z calculated and observed, MS/MS data, and their comparative profile for two varieties of *Dracocephalum* are summarized in Table 1. The total ion chromatograms of *D. ruyschiana* L. extracts in positive and negative ionization modes are presented in Figure 2, respectively.

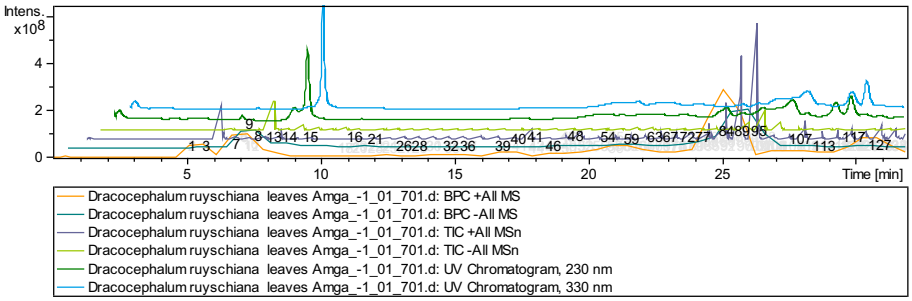

Fig. 2. Chemical profiles of *D. ruyschiana* L. sample represented total ion chromatogram.

Table 1. Compounds identified from the extracts of *D. palmatum* Stephan and *D. ruyschiana* L. in positive and negative ionization modes by HPLC-ion trap-MS/MS.

№	Variety of *Dracocephalum*	Identified compounds	Formula	Mass	Molecular ion $[M-H]^-$	Molecular ion $[M+H]^+$	2-nd fragmentation MS/MS	3-rd fragmentation MS/MS	4-th fragmentation MS/MS	References
1	*D. palmatum*	Perillic acid	$C_{10}H_{14}O_2$	166.217		167	149	121		[41]
2	*D. ruyschiana*	Caffeic acid	$C_9H_8O_4$	180.1574		181	135	119		[9; 11; 18; 25; 26]
3	*D. palmatum*	Methylgallic acid [Methyl gallate]	$C_8H_8O_5$	184.1461	183		139	137	119	[1; 25; 27]
4	*D. ruyschiana*	Hydroxy methoxy dimethylbenzoic acid	$C_{10}H_{12}O_4$	196.1999		197	179	161	133	[10]
5	*D. ruyschiana*	L-Tryptophan [Tryptophan; (S)-Tryptophan]	$C_{11}H_{12}N_2O_2$	204.2252		205	188	144	118	[19; 23; 24]
6	*D. ruyschiana*	Pinosylvin [3,5-Stilbenediol; Trans-3,5-Dihydroxystilbene]	$C_{14}H_{12}O_2$	212.2439		213	168	126		[4; 28]
7	*D. palmatum*	5-Methoxydimethyltryptamine	$C_{13}H_{18}N_2O$	218.2948		219	201	159; 118		[24]
8	*D. ruyschiana*	Resveratrol [trans-Resveratrol; 3,4',5-Trihydroxystilbene; Stilbentriol]	$C_{14}H_{12}O_3$	228.2433		229	142; 210	114		[10; 43]
9	*D. palmatum*	Hydroxy dodecanoic acid	$C_{12}H_{22}O_3$	246.3001		247	229	216		[10]
10	*D. palmatum*	Hexadecatrienoic acid [Hexadeca-2,4,6-trienoic acid]	$C_{16}H_{26}O_2$	250.3764		251	233; 191	187		[10]
11	*D. ruyschiana*	Ketoprofen [Orudis; 2-(3-Benzoylphenyl)Propionic acid; Profenid]	$C_{16}H_{14}O_3$	254.2806	253		210	180		[40]
12	*D. ruyschiana*	Apigenidin	$C_{15}H_{11}O_4$	255.2454		256	168	122		[26]
13	*D. palmatum; D. ruyschiana*	Apigenin [5,7-Dixydroxy-2-(40Hydroxyphenyl)-4H-Chromen-4-One]	$C_{15}H_{10}O_5$	270.2369		269	225	181	117	[3; 18]
14	*D. palmatum*	Oleic acid (Cis-9-Octadecenoic acid; Cis-Oleic acid)	$C_{18}H_{34}O_2$	282.4614		283	209; 114			[4; 13]
15	*D. ruyschiana*	Luteolin	$C_{15}H_{10}O_6$	286.2363		287	286; 153	171	153	[2; 18; 25]
16	*D. palmatum*	Kaempferol [3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one]	$C_{15}H_{10}O_6$	286.2363		287	269; 202	233; 205	216	[1; 9; 39]
17	*D. palmatum*	Dihydrokaempferol [Aromadendrin; Katuranin]	$C_{15}H_{12}O_6$	288.2522	287		269; 151	267; 183	211	[10; 24]
18	*D. palmatum*	Mesembrenol	$C_{17}H_{23}NO_3$	289.3694		290	242; 122	184; 149		[21]

19	*D. ruyschiana*	(epi)catechin	$C_{15}H_{14}O_6$	290.2681		291	273; 117	255; 145		[9; 10; 24; 43]
20	*D. ruyschiana*	Ellagic acid [Benzoaric acid; Elagostasine; Lagistase; Eleagic acid]	$C_{14}H_6O_8$	302.1926	301		284	221	112	[1; 25; 30]
21	*D. palmatum*	Tanshinone IIB [(S)-6-(Hydroxymethyl)-1,6-Dimethyl-6,7,8,9-Tetrahydrophenanthro[1,2-B]Furan-10,11-Dione]	$C_{19}H_{18}O_4$	310.3438		311	283; 137	119		[42]
22	*D. palmatum*	Petunidin	$C_{16}H_{13}O_{7+}$	317.2702		318	166; 300	121		[10]
23	*D. ruyschiana*	1-O-(4-Coumaroyl)-glucose	$C_{15}H_{18}O_8$	326.2986	325		145	117		[9; 22]
24	*D. ruyschiana*	9,10-Dihydroxy-8-oxooctadec-12-enoic acid [oxo-DHODE; oxo-Dihydroxy-octadecenoic acid]	$C_{18}H_{32}O_5$	328.4437	327		229	209	183	[36]
25	*D. ruyschiana*	Docosahexaenoic acid	$C_{22}H_{32}O_2$	328.4883	327		309; 201	291; 171	273	[34]
26	*D. ruyschiana*	Caffeoylshikimic acid [5-O-Caffeoylshikimate]	$C_{16}H_{15}O_8$	335.2855	335		179	135	133	[27; 31]
27	*D. palmatum*	Salvianolic acid G	$C_{18}H_{12}O_7$	340.2837		341	296; 208	278; 208	235; 164	[11; 41]
28	*D. palmatum*	1-Caffeoyl-beta-D-glucose [Caffeic acid-3-O-beta-D-glucoside]	$C_{15}H_{18}O_9$	342.298	341		178; 119	135		[9; 19]
29	*D. palmatum; D. ruyschiana*	Caffeic acid-O-hexoside [Caffeoyl-O-hexoside]	$C_{15}H_{18}O_9$	342.298	341		178; 113			[27; 31; 36]
30	*D. ruyschiana*	Apigenin 7-sulfate	$C_{15}H_{10}O_8S$	350.3001	349		269	223		[10; 33]
31	*D. palmatum*	Hinokinin	$C_{20}H_{18}O_6$	354.3533		355	337; 189	319; 226		[5; 26]
32	*D. palmatum*	Prolithospermic acid	$C_{18}H_{14}O_8$	358.2990		359	341; 207	314; 267; 149		[11; 41]
33	*D. palmatum*	Rosmarinic acid	$C_{18}H_{16}O_8$	360.3148	359		161	133		[11; 18; 41]
34	*D. ruyschiana*	Caffeic acid derivative	$C_{16}H_{18}O_9Na$	377.2985	377		341; 215	179		[6]
35	*D. palmatum*	Salvianic acid C	$C_{18}H_{18}O_9$	378.3301	377		359; 315	289	229	[11]
36	*D. palmatum*	Dimethyl-secoisolariciresinol	$C_{22}H_{30}O_6$	390.4700		391	373; 249; 121	355; 225	313; 226	[5]
37	*D. palmatum*	Caffeic acid derivative		408		409	365; 241	241		[27]
38	*D. palmatum*	Podophyllotoxin	$C_{22}H_{22}O_8$	414.4053		415	248; 331	145		[5]
39	*D. ruyschiana*	Chrysin 6-C-glucoside	$C_{21}H_{20}O_9$	416.3781		417	51; 127	333; 267	165	[19]
40	*D. ruyschiana*	Apocarotenal [(all-E)-beta-apo-caroten-8'-al]	$C_{30}H_{40}O$	416.6380		417	399; 200	351	267	[14]
41	*D. ruyschiana*	Chrysin glucuronide	$C_{21}H_{18}O_{10}$	430.3616		431	255	255; 153	171	[10]
42	*D. palmatum; D. ruyschiana*	Pelargonidin-3-O-glucoside (callistephin)	$C_{21}H_{21}O_{10}$	433.3854		433	271	153; 225	171	[3; 30]
43	*D. palmatum*	Prunin [Naringenin-7-O-glucoside]	$C_{21}H_{22}O_{10}$	434.3934	433		271; 151	269; 151		[9; 18]
44	*D. palmatum*	Luteolin 7-O-glucoside [Cynaroside; Luteoloside]	$C_{21}H_{20}O_{11}$	448.3769		449	287; 199	153		[2; 9; 19; 31]
45	*D. palmatum*	Astragalin [Kaempferol 3-O-glucoside]	$C_{21}H_{20}O_{11}$	448.3769	447		285; 327	241	199	[2; 9; 24; 31; 38]
46	*D. ruyschiana*	Apigenin 7-O-glucuronide	$C_{21}H_{18}O_{11}$	446.361		447	271	153	271; 171	[6; 31]

47	*D. palmatum; D. ruyschiana*	Eriodictyol-O-hexoside	$C_{21}H_{22}O_{11}$	450.3928	449		285; 151	243; 151		[1; 10]
48	*D. ruyschiana*	Acacetin 7-O-beta-D-glucuronide	$C_{22}H_{20}O_{11}$	460.3876	459		283; 343; 175	268	267	[16]
49	*D. ruyschiana*	Luteolin-7-O-beta-glucuronide	$C_{21}H_{18}O_{12}$	462.3604		463	287	268	245; 119	[35; 41]
50	*D. ruyschiana*	Kaempferol-3-O-glucuronide	$C_{21}H_{18}O_{12}$	462.3604		463	287	268; 169	241; 119	[1; 9; 10; 27]
51	*D. ruyschiana*	Diosmetin-7-O-beta-glucoside	$C_{22}H_{22}O_{11}$	462.4035		463	287	168	123	[16; 20]
52	*D. palmatum*	Peonidin-3-O-glucoside	$C_{22}H_{23}O_{11+}$	463.4114		463	301	286	258; 140	[9; 30]
53	*D. palmatum*	Cyanidin 3-(acetyl)hexose	$C_{23}H_{23}O_{12+}$	491.4215		491	287	245; 153	171	[37]
54	*D. ruyschiana*	3,4-O-dicaffeoylquinic acid [Isochlorogenic acid B]	$C_{25}H_{24}O_{12}$	516.4509		517	397	337; 135		[2; 31]
55	*D. palmatum*	2'-Hydroxygenistein O-glucoside malonylated	$C_{24}H_{22}O_{14}$	534.4231	533		489	285; 326	284	[38]
56	*D. palmatum*	Luteolin 7-O-beta-D-(6"-O-malonyl)-glucoside	$C_{24}H_{22}O_{14}$	534.4231		535	436; 354; 287; 214	328; 238		[7; 16]
57	*D. palmatum*	Acacetin C-glucoside methylmalonylated	$C_{26}H_{26}O_{13}$	546.4758		547	529; 496; 369	343		[38]
58	*D. palmatum*	5,8-epoxy-alpha-carotene	$C_{40}H_{56}O$	552.872		553	536; 412; 207	299; 261		[8]
59	*D. ruyschiana*	Apigenin 8-C-pentoside-6-C-hexoside	$C_{26}H_{28}O_{14}$	564.4921		565	547; 274	529; 474; 247	390	[3]
60	*D. palmatum*	Kaempferol 3-O-rutinoside	$C_{27}H_{30}O_{15}$	594.5181	593		285	241; 199	199	[1; 2; 9; 24; 27; 31]
61	*D. ruyschiana*	Violaxanthin [Zeaxanthin Dieperoxide]	$C_{40}H_{56}O_4$	600.8702		601	364; 582	346; 202; 142	114	[17]

4 Discussion

There were identified 61 target analytes in extracts of *D. palmatum* Stephan and *D. ruyschiana* L. In the present study, 47 polyphenol compounds were identified and characterized including 14 flavones (Apigenidin, apigenin, luteolin, apigenin 7-sulfate, chrysin 6-*C*-glucoside, chrysin glucuronide, apigenin 7-*O*-glucuronide, luteolin 7-*O*-glucoside, Acacetin 7-*O*-*β*-D-glucuronide, Apigenin 8-*C*-pentoside-6-*C*-hexoside, 5 flavonols (kaempferol, dihydrokaempferol, astragalin, Kaempferol-3-O-glucuronide, Kaempferol 3-*O*-rutinoside, 2 flavanones (Prunin, Eriodictyol-*O*-hexoside), 1 isoflavone (2'-Hydroxygenistein *O*-glucoside malonylated), 1 flavan-3-ol ((epi)catechin), 4 anthocyanidins (Petunidin, Pelargonidin-3-*O*-glucoside (callistephin), Peonidin-3-*O*-glucoside, Cyanidin 3-(acetyl)hexose), 3 lignans (hinokinin, Dimethyl-secoisolariciresinol, Podophyllotoxin), 2 stilbenes and 15 phenolic acids.

Figures 3-4 shows examples of the decoding spectra (collision-induced dissociation (CID) spectrum) of the ion chromatogram obtained using tandem mass spectrometry. The $[M + H]^+$ ion produced three fragment ions at *m/z* 373, *m/z* 248, and *m/z* 121 (Fig. 3). The fragment ion with *m/z* 373 yields two daughter ions at *m/z* 355, and *m/z* 255. The fragment ion with *m/z* 355 yields two daughter ions at *m/z* 313, and *m/*z 226. This compound was identified in the bibliography as Dimethyl-secoisolariciresinol in extracts from lignans [5].

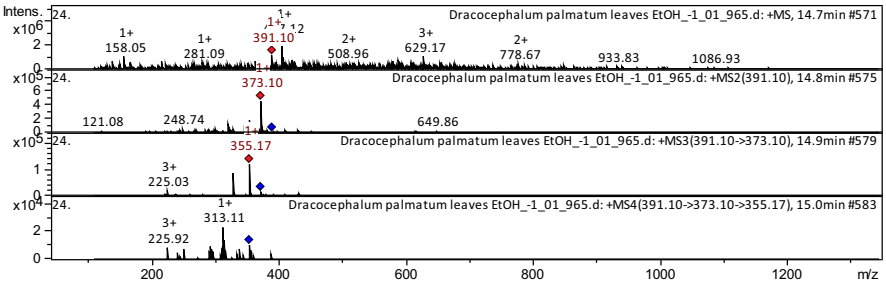

Fig. 3. Mass spectrum of dimethyl-secoisolariciresinol from extracts of D. palmatum, *m/z* 391.10.

The mass spectrum in positive ion mode of L-tryptophan from extracts of *D. ruyschiana* is shown in Figure 4. The [M + H]+ ion produced one fragment ions at *m/z* 188.02 (Fig. 4). The fragment ion with *m/z* 188.02 yields one daughter ion at *m/z* 144.05. The fragment ion with *m/z* 144.05 yields one daughter ion at *m/z* 118.08. To our knowledge, L-tryptophan was reported in *Passiflora incarnata* [19]; *Vigna unguiculata* [23]; *Camellia kucha* [24].

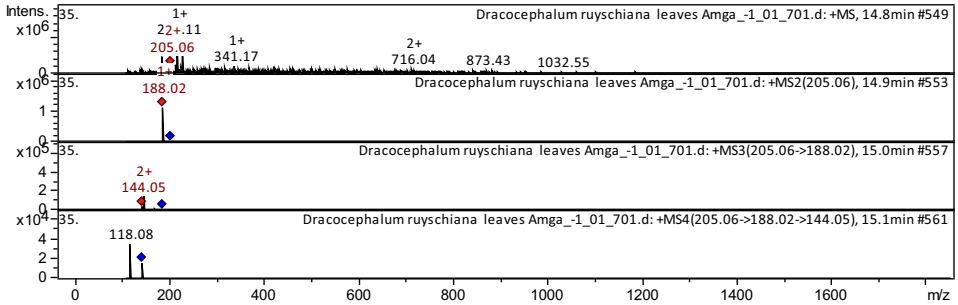

Fig. 4. Mass spectrum of L-tryptophan from extracts of *D. ruyschiana*, *m/z* 205.

Thus, 61 metabolome compounds were identified in the maceration extracts of *D. palmatum* Stephan and *D. ruyschiana* L., many of which are characteristic of genus *Dracocephalum*. Of these, 53 components were identified for the first time in this plant species. These are flavones: Apigenin 8-*C*-pentoside-6-*C*-hexoside, Apigenin 7-sulfate; Chrysin 6-*C*-glucoside, Chrysin glucuronide; flavanols: Kaempferol, Dihydrokaempferol, Astragalin; flavan-3-ol (epi)Catechin, phenolic acids: Methylgallic acid; Hydroxy methoxy dimethylbenzoic acid; Ellagic acid; Caffeoylshikimic acid; Prolithospermic acid; 3,4-*O*-dicaffeoylquinic acid; salvianolic acid G; stilbenes pinosylvin and resveratrol; anthocyanins petunidin, Pelargonidin-3-*O*-glucoside; Peonidin-3-*O*-glucoside; Cyanidin 3-(acetyl)hexose; perillic acid; lignans: Hinokinin, Dimethyl-secoisolariciresinol, Podophyllotoxin, carotenoids: Apocarotenal, 5,8-epoxy-alpha-carotene; etc.

5 Conclusion

The extracts of *D. palmatum* Stephan and *D. ruyschiana* L. contains a large number of polyphenolic complexes, which are biologically active compounds. For the most complete and safe extraction, the method of maceration with MeOH was used. To identify target analytes in supercritical extracts, HPLC was used in combination with a BRUKER DALTONIKS ion trap. The results of a preliminary study showed the presence of 61 compounds corresponding to the genus Dracocephalum, of which 53 were identified for the first time in *Dracocephalum*.

The data obtained will help to intensify future research on the development and production of various medical products containing targeted extracts of *D. palmatum* Stephan and *D. ruyschiana* L. A wide variety of biologically active polyphenolic compounds opens up rich opportunities for the creation of new drugs, as well as biologically active additives based on extracts from the genus Dracocephalum.

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References

1. I.M. Abu-Reidah, M. S. Ali-Shtayeh, R. M. Jamous, D. Arraes-Roman, A. Segura-Carretero, Food Chem., **166**, 179 (2015)
2. Z. Cai, C. Wang, L. Zou, X. Liu, J. Chen, M. Tan, Y. Mei, L. Wei, Molecules, **24**, 1936 (2019)
3. G. Dinelli, A. Segura-Carretero, R. Di Silvestro, I. Marotti, D. Arraez-Roman, S. Benedettelli, L. Ghiselli, A. Fernandez-Gutierrez, J. Chromatogr. A., **1218** (2011)
4. D. Ekeberg, P.-O. Flate, M. Eikenes, M. Fongen, C.F. Naess-Andresen, J. of Chromatogr. A, **26**7 (2006)
5. P.C. Eklund, M. J. Backman, L.A. Kronberg, A.I. Smeds, R.E. Sjoholm, J. of Mass Spectr., **43**, 97 (2008)
6. El-Sayed, M.A. Abbas, F.A. Refaat, S. El-Shafae, A.M. Fikry, E. Egyptian J. of Chem., **22**, 2 (2021)
7. K.H. Enerstvedt, M. Jordheim, O.M. Andersen, American J. of Plant Science, **7** (2016)
8. L. Etzbach, A. Pfeiffer, F. Weber, A. Schieber, Food Chem., **245** (2018)
9. P. Goufo R.K. Singh, I. A. Cortez, Antioxidants, **9** (2020)
10. A.R. Hamed, S.S. El-Hawary, R.M. Ibrahim, U.R. Abdelmohsen, A.M. El-Halawany, J. Chrom. Sci., **1** (2020)
11. R.-W. Jiang, K.-M. Lau, P.-M. Hon, T.C.W. Mak, K.-S. Woo, K.-P. Fung, Current Med. Chem., **12**, 237 (2005)
12. J. Kim, J.N. Kim, I. Park, S. Sivtseva, Z. Okhlopkova, I.S. Zulfugarov, S.-W. Kim, Oncology Reports, **44** (2020)
13. S. Kim, S. Oh, H.B. Noh, S. Ji, S.H. Lee, J.M. Koo, C.W. Choi, H.P. Jhun, Molecules, **23** (2018)
14. S. Lara-Abia, G. Lobo-Rodrigo, J. Welti-Chanes, M. Pilar Cano, Roots. Foods, **10** (2021)
15. S.-E. Lee, Z. Okhlopkova, C. Lim, S. Cho, Chinese J. of Nat. Med., **18**, 10 (2020)
16. M. Martinez-Vazquez, R. Estrada-Reyes, A. Martinez-Laurrabaquio, C. Lopez-Rubalcava, G. Heinze, J. of Ethnopharmacol, **141** (2012)
17. A.Z. Mercadante, D.B. Rodrigues, F.C. Petry, L.R. Barros Mariutti, Food Research International, **99**, 2 (2017)
18. D.O. Olennikov, N.K. Chirikova, Z.M. Okhlopkova, Molecules, **18** (2013)

19. M. Ozarowski, A. Piasecka, A. Paszel-Jaworska, D. Siqueira de A. Chaves, A. Romaniuk, M. Rybczynska, A. Gryszczynska, A. Sawikowska, P. Kachlicki, P.L. Mikolajczak, A. Seremak-Mrozikiewicz, Braz. J. Pharmacol, **28** (2018)
20. B.P. Pandey, S.P. Pradhan, K. Adhikari, Chemistry & Biodiversity, **17**, 6 (2020)
21. S. Patnala, I. Kanfer, J. Pharm. Pharm. Sci., **18**, 4 (2015)
22. L. Paudel, F. J. Wyzgoski, J. C. Scheerens, A. M. Chanon, R. N. Reese, D. Smiljanic, C. Wesdemiotis, J. J. Blakeslee, K. M. Riedl, P. L. Rinaldi, J. Agr. Food Chem., **61**, 49 (2013)
23. I. Perchuk, T. Shelenga, M. Gurkina, E. Miroshnichenko, M. Burlyaeva, Molecules, **25** (2020)
24. D. Qin, Q. Wang, H. Li, X. Jiang, K. Fang, Q. Wang, B. Li, C. Pan, H. Wu, Food Research International, **138** (2020)
25. S.A.O. Santos, C.S.R. Freire, M.R.M. Domingues, A.J.D. Silvestre, C.P. Neto, Food Chem., **59** (2011)
26. M. Sharma, R. Sandhir, A. Singh, P. Kumar, A. Mishra, S. Jachak, S.P. Singh, J. Singh, J. Roy, Front. Plant. Sci.**, 7** (2016)
27. V. Spinola, J. Pinto, P.C. Castilho, Food Chem., **173**, 14 (2015)
28. F. Simard, J. Legault, S. Lavoie, V. Mshvildadze, A. Pichette, Phytother. Res., **22**, 919 (2008)
29. State Pharmacopoeia of the Russian Federation, 13th edition (2018)
30. J. Sun, X. Liu, T. Yang, J. Slovin, P. Chen, Food Chem., **146**, 289 (2014)
31. L. Sun, S. Tao, S. Zhang, Molecules, **24**, 159 (2019)
32. M. Talari, E. Seydi, A. Salimi, et al., Biomed Res. Int. (2014)
33. Y.C.E. Teles, C.C. Rebello Horta, M. de Fatima Agra, W. Siheri, M. Boyd, J. O. Igoli, A.I. Gray, M. de Fatima Vanderlei de Souza, Molecules, **20** (2015)
34. M.C. Thomas, S.R. Dunn, J. S. Altvater, G. Dove, G.W. Nette, Anal. Chem., **84** (2012)
35. N. E. Thomford, K. Dzobo, D. Chopera, A. Wonkam, A. Maroyi, D. Blackhurst, C. Dandara, Molecules, **21**, 7 (2016)
36. L. Van Hoyweghen, K. De Bosscher, G. Haegeman, D. Deforce, A. Heyerick, Phytotherapy Res. (2013)
37. V. Vera de Rosso, S. Hillebrand, E. Cuevas Montilla, F.O. Bobbio, P. Winterhalter, A.Z. Mercadante, J. of Food Comp. and Analys, **21** (2008)
38. A. Wojakowska, A. Piasecka, P.M. Garcia-Lopez, F. Zamora-Natera, P. Krajewski, L. Marczak, P. Kachlicki, M. Stobiecki, Phytochem., **92**, 71 (2013)
39. J. Xiao, T. Wang, P. Li, R. Liu, Q. Li, K. Bi, Journal of Chromatography, **1028**, 33 (2016)
40. J. Xie, C. Ding, Q. Ge, Z. Zhou, X. Zhi, J. of Chromatogr. B., **864**, 87 (2008)
41. L. L. Xu, J. J. Xu, K. R. Zhong, Z. P. Shang, F. Wang, R. F. Wang, B. Liu, Molecules, **22** (2017)
42. S. T. Yang, X. Wu, W. Rui, J. Guo, Y. F. Feng, Acta Chromatographica, **27** (2015)
43. Z.-W. Zhu, J. Li, X.-M. Gao, E. Amponsem, L.-Y. Kang, L.-M. Hu, B.-L Zhang. Y.-X. Chang, J. of pharmaceut. and biomedical analys, **62**, 162 (2012)