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Original scientific paper

THE QUANTITATIVE STRUCTURE-RETENTION RELATIONSHIP OF THE GC-MS PROFILE OF YARROW ESSENTIAL OIL

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In the essential oil of yarrow (Achillea millefolium L. sensu lato) collected from natural population on Mt. Rtanj (Serbia) and distilled by Clevenger apparatus 104 compounds were detected, and the most abundant were camphor (9.8%), caryophyllene oxide (6.5%), terpinen-4-ol (6.3%) and 1,8-cineole (5.6%). The quantitative structure-retention relationship (QSRR) model was employed to predict the retention indices, using four molecular descriptors selected by factor analysis and a genetic algorithm. The coefficients of determination reached the value of 0.862, demonstrating that this model could be used for prediction purposes.

Keywords: *Achillea millefolium* L., retention indices, molecular descriptors, factor analysis, genetic algorithm, coefficients of determination.

INTRODUCTION

Genus *Achillea* (Asteraceae family), commonly known as yarrow, includes more than 100 perennial species, which mostly grow spontaneously throughout Europe and Asia. There are 19 species reported in Serbia (1). *Millefolium* group is characterized by a wide morphological, cytological and chemical diversity (2). Furthermore, these species have the tendency to hybridize and to vary in phenotype according to the environmental conditions (3). Common yarrow (*Achillea millefolium* L. *sensu lato*) is considered to be aggregate. In the Flora of Serbia, three subspecies are reported: subsp. *pannonica*, subsp. *millefolium* and subsp. *collina* with two forms (f. *colina* with white flowers and f. *rubriflora* with pink flowers) (1). Yarrow with white flowers (*Millefolii herba*) has been used in traditional medicine since the ancient times. Throughout Euro-Asian region it is widely used for treating gastrointestinal complaints as a bitter aromatic and to stimulate the secretion of bile, as well as an antispasmodic, emenagogue and febrifuge (4). Yarrow has been used in Serbian traditional medicine for treating hemorrhoids and to improve wound healing (external application). These applications are mentioned in other traditional medicine as well (5), corroborated by experiments (6). Modern scientific investigations show that it possesses anti-inflammatory (7), antioxidant and antibacterial activities (8, 9), as well as antican-

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cer properties (10). The aim of this investigation is to determine essential oil composition of *A. millefolium sensu lato* from Mt Rtanj and to develop a QSRR model for predicting the retention times of chemical compounds from the essential oil.

MATERIAL AND METHODS

The aerial parts of *A. millefolium* (~35 cm) was collected on 7th July 2018, from natural population on Mt. Rtanj at full flowering stage. Voucher specimens were deposited in the Herbarium of the University of Novi Sad (BUNS) under the acquisition number 2-1449.

A total of 20.0 g of cut *A. millefolium* aerial parts was placed in a 1000 mL round-bottomed flask and 500 mL of water was added and the flask was then connected to Clevenger apparatus. The distillation was done at a rate of 2-3 mL/min for 2h. At the end of the process 0.16% of pale yellow essential oil was obtained, which was analyzed by GC (HP 5890) coupled to an MS (HP 5973 MSD) and fitted with a capillary column HP-5MS. Terms and conditions are described in detail in the previous paper (11).

Obtained results of GC-MS analysis of *A. millefolium* essential oil were used for quantitative structure retention relationship (QSRR) analysis, artificial neural network (ANN) modeling as well as for global sensitivity analysis (12). The determination of molecular descriptors (MDs) was performed using the PaDel-descriptor software (13). The most relevant MDs for RIs prediction by factor analysis and genetic algorithm (GA), using Heuristic Lab software. Statistical investigation of the data was performed by the Statistica 10 software. Multi-layer perceptron architecture (MLP) was used to build the ANN for prediction of RIs for compounds found in *A. millefolium* essential oil. Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm was used to speed-up the calculation of weight coefficients of the ANN (11). The observed data were randomly separated to 60%, 20% and 20% of data used for training, testing and validations, respectively (12). Yoon's global sensitivity equation was used to calculate the relative impact of the chosen MDs on RIs, according to weight coefficients of the developed ANN (14).

RESULTS AND DISCUSSION

In the *A. millefolium* essential oil, a total of 104 compounds were detected, which represented 96.4% of the total oil composition (Table 1). Among these compounds, 20 were not identified compounds (NI), which compromised 15.3%. However, relative intensity of molecular ions peaks (m/z) for all NI compounds were given in Table 1. As it can be seen from the table, the most abundant compounds in *A. millefolium* essential oil were camphor (9.8%), caryophyllene oxide (6.5%), terpinen-4-ol (6.3%) and 1,8-cineole (5.6%). Oxygenated monoterpenes and sesquiterpenes with 28.1% and 23.6%, respectively, were dominant in the chemical composition, followed by monoterpene and sesquiterpene hydrocarbons with 14.2% and 11.2%, respectively.

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Table 1. Chemical composition of *A. millefolium* aerial parts and molecular descriptors

No	Compound	RI[a]	RI[b]	$RI_{pred.}$	%	GATS5e	Mv	VE1_Dt	MWC9
1	α-Thujene	928	924	866.121	0.2	0.562	0.551	0.203	10.807
2	α-Pinene	935	932	1284.488	0.7	0.762	0.551	0.005	10.594
3	Camphene	949	946	1334.457	0.4	0.431	0.551	0.084	10.543
4	Sabinene	974	969	949.974	2.8	0.594	0.551	0.203	10.807
5	β-Pinene	978	974	1283.501	1.5	0.766	0.551	0.005	10.594
6	dehydro-1,8-Cineole	991	988	1131.366	0.2	0.145	0.557	0.066	10.521
7	α-Terpinene	1015	1014	1128.345	0.4	0.757	0.551	0.165	9.434
8	p-Cymene	1022	1020	987.050	0.9	0.876	0.575	0.165	9.434
9	Limonene	1027	1024	928.663	0.1	0.666	0.551	0.165	9.434
10	1,8-Cineole	1028	1026	1143.515	5.6	0.132	0.538	0.066	10.521
11	γ-Terpinene	1052	1054	1098.075	1.1	0.745	0.551	0.165	9.434
12	cis-Sabinene hydrate	1060	1065	1136.628	0.4	0.633	0.531	0.203	10.807
13	Terpinolene	1080	1086	893.172	0.3	0.646	0.551	0.165	9.434
14	Linalool	1092	1095	1018.278	4.2	0.489	0.538	0.110	9.125
15	n-Nonanal	1096	1100	1105.060	0.2	0.835	0.521	0.000	8.043
16	NI-1	1107	-	-	2.5	-	-	-	-
17	cis-p-Menth-2-en-1-ol	1113	1118	1308.579	0.2	0.473	0.538	0.112	9.795
18	Chrysanthenone	1116	1124	923.006	0.2	2.406	0.580	0.002	10.827
19	trans-Pinocarveol	1132	1135	1304.882	0.1	0.775	0.557	0.020	10.750
20	trans-p-Menth-2-en-1ol	1133	1136	1296.376	0.1	0.813	0.531	0.165	9.434
21	Camphor	1138	1141	1372.125	9.8	1.300	0.557	0.078	10.917
22	NI-2	1150	-	-	0.3	-	-	-	-
23	Pinocarvone	1155	1160	1301.057	0.7	0.838	0.580	0.020	10.750
24	Borneol	1159	1165	1510.630	1.6	1.148	0.538	0.078	10.917
25	NI-3	1160	-	-	0.2	-	-	-	-
26	cis-Pinocamphone	1167	1172	1316.178	0.1	0.727	0.557	0.020	10.750
27	Terpinen-4-ol	1173	1174	1186.422	6.3	0.209	0.538	0.242	9.931
28	Thuj-3-en-10-al	1179	1181	1079.573	0.1	0.768	0.538	0.245	9.795
29	α-Terpineol	1186	1190	1088.580	1.3	1.277	0.557	0.042	10.667
30	Myrtenol	1189	1194	1247.659	0.2	1.426	0.580	0.042	10.667
31	Myrtenal	1191	1195	1223.580	0.4	0.900	0.567	0.084	9.992
32	cis-Carveol	1226	1226	1334.126	0.1	0.751	0.557	0.132	9.732
33	trans-Chrysanthenyl acetate	1231	1235	1129.230	0.2	1.430	0.572	0.018	10.994
34	Cumin aldehyde	1235	1238	1348.877	0.1	0.858	0.607	0.117	9.560
35	cis-Chrysanthenyl acetate	1257	1261	1129.230	0.4	1.430	0.572	0.018	10.994
36	Bornyl acetate	1282	1287	1235.626	0.4	0.996	0.554	0.012	11.061
37	Thymol	1288	1289	1372.639	0.6	2.548	0.580	0.119	9.756
38	Carvacrol	1298	1298	1252.284	1.1	0.942	0.580	0.132	9.732
39	p-Mentha-1,4,-dien-7-ol	1325	1325	1428.156	0.2	0.853	0.557	0.117	9.560
40	trans-Carvyl acetate	1334	1339	1254.619	0.1	0.815	0.572	0.009	10.022
41	Eugenol	1354	1356	1493.266	0.1	1.230	0.612	0.046	9.735
42	cis-Carvyl acetate	1359	1365	1254.619	0.1	0.815	0.572	0.009	10.022
43	α-Copaene	1373	1374	1504.613	0.1	1.007	0.551	0.098	11.349
44	β-Bourbonene	1382	1387	1507.414	0.1	0.932	0.551	0.095	11.355
45	cis-Jasmone	1395	1392	1322.328	0.1	1.226	0.573	0.046	9.773
46	Methyl eugenol	1401	1403	1428.597	0.1	1.485	0.601	0.058	9.856
47	trans-Caryophyllene	1418	1417	1320.696	4.7	0.963	0.551	0.032	10.671
48	cis-β-Farnesene	1441	1440	1548.775	0.1	0.841	0.551	0.012	9.162
49	α-Humulene	1451	1452	1537.107	0.7	0.930	0.551	0.084	9.783
50	trans-β-Farnesene	1455	1454	1548.775	0.1	0.841	0.551	0.012	9.162
51	9-epi-trans-Caryophyl-lene	1459	1464	1320.696	0.4	0.963	0.551	0.032	10.671
52	γ-Muurolene	1473	1478	1586.163	0.3	0.984	0.551	0.109	10.550
53	Germacrene D	1480	1484	1562.301	2.9	0.941	0.551	0.103	9.733
54	β-Selinene	1484	1489	1573.418	0.2	0.884	0.551	0.109	10.651

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Table 1. Continuation.

No	Compound	RI[a]	RI[b]	$RI_{pred.}$	%	GATS5e	Mv	VE1_Dt	MWC9
55	trans-Muurola-4(14),5-diene	1490	1493	1591.800	0.1	1.077	0.551	0.109	10.550
56	epi-Cubebol	1493	1493	1567.126	0.5	0.856	0.555	0.109	11.652
57	γ-Cadinene	1512	1513	1586.163	1.1	0.984	0.551	0.109	10.550
58	α-Calacorene	1540	1544	1600.514	0.3	1.100	0.583	0.109	10.550
59	Elemol	1546	1548	1532.135	0.7	0.703	0.542	0.132	10.623
60	trans-Nerolidol	1560	1561	1428.523	0.1	0.467	0.542	0.085	9.517
61	NI-4	1565	-	-	0.2	-	-	-	-
62	NI-5	1571	-	-	0.4	-	-	-	-
63	ar-Tumerol	1575	1582	1621.097	0.6	2.104	0.570	0.257	9.954
64	Caryophyllene oxide	1580	1582	1331.415	6.5	0.579	0.555	0.015	11.141
65	NI-6	1584	-	-	0.2	-	-	-	-
66	Viridiflorol	1587	1592	1416.937	0.5	0.921	0.542	0.067	11.406
67	Ledol	1596	1602	1416.937	0.1	0.921	0.542	0.067	11.406
68	Humulene epoxide II	1603	1608	1474.255	0.6	0.626	0.555	0.072	10.652
69	NI-7	1605	-	-	0.2	-	-	-	-
70	NI-8	1622	-	-	0.3	-	-	-	-
71	γ-Eudesmol	1626	1630	1114.227	1.5	0.580	0.542	0.185	10.789
72	Caryophylla-4(12), 8(13)-dien-5-α-ol	1631	1639	1376.326	1.8	0.691	0.555	0.035	10.758
73	α-Muurolol (=Torreyol)	1636	1640	1547.839	3.3	0.839	0.542	0.076	10.772
74	NI-9	1641	-	-	0.2	-	-	-	-
75	β-Eudesmol	1646	1649	1365.178	2.4	0.699	0.542	0.185	10.789
76	α-Cadinol	1648	1652	1547.839	1.2	0.839	0.542	0.076	10.772
77	NI-10	1653	-	-	0.3	-	-	-	-
78	NI-11	1664	-	-	4.3	-	-	-	-
79	NI-12	1667	-	-	0.5	-	-	-	-
80	NI-13	1670	-	-	0.2	-	-	-	-
81	α-Bisabolol	1678	1685	1590.963	0.3	0.961	0.542	0.205	10.136
82	Germacra-4(15),5, 10(14)-trien-1-α-ol	1681	1685	1377.912	1.7	0.733	0.555	0.098	9.930
83	NI-14	1686	-	-	4.0	-	-	-	-
84	NI-15	1700	-	-	0.2	-	-	-	-
85	NI-16	1707	-	-	0.3	-	-	-	-
86	Curcuphenol	1711	1717	1534.119	0.2	1.952	0.570	0.148	10.041
87	2Z,6E-Farnesol	1715	1713	1845.951	0.2	1.186	0.542	0.010	9.240
88	Chamazulene	1724	1730	1512.019	0.1	1.048	0.611	0.057	10.419
89	6R,7R-Bisabolone	1739	1740	1600.565	1.2	1.979	0.555	0.148	10.041
90	β-Costol	1761	1765	1535.495	0.3	0.841	0.555	0.152	10.695
91	NI-17	1779	-	-	0.2	-	-	-	-
92	2-Pentadecanone, 6,10,14-trimethyl-	1840	1847	2133.804	0.2	0.643	0.518	0.000	9.459
93	NI-18	1903	-	-	0.3	-	-	-	-
94	Heptadecanal	1913	1922	1929.535	0.1	0.704	0.518	0.000	8.883
95	NI-19	1945	-	-	0.2	-	-	-	-
96	Heneicosane	2100	2100	2148.124	0.2	0.973	0.506	0.000	9.076
97	Phytol	2123	2122	2404.862	0.1	1.057	0.517	0.007	9.594
98	9,12-Octadecadienoic acid (Z,Z)-	2148	2132	1961.330	0.1	0.736	0.535	0.029	9.103
99	trans-Geranylgeraniol	2172	2181	1576.040	0.3	1.108	0.544	0.007	9.594
100	NI-20	2226	-	-	0.3	-	-	-	-
101	Tricosane	2301	2300	2216.401	0.6	0.975	0.507	0.000	9.187
102	Pentacosane	2497	2500	2277.141	0.4	0.978	0.508	0.000	9.287
103	Heptacosane	2701	2700	2627.325	0.2	0.000	1.000	0.000	9.377
104	Nonacosane	2909	2900	2626.827	0.3	0.000	1.000	0.000	9.460
Monoterpene hydrocarbons					14.2				
Oxygenated monoterpenes					28.1				

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Table 1. Continuation.

No	Compound	RI[a]	RI[b]	$RI_{pred.}$	%	GATS5e	Mv	VE1_Dt	MWC9
Sesquiterpene hydrocarbons					11.2				
Oxygenated sesquiterpenes					23.6				
Oxygenated diterpenes					0.3				
Other[c]					2.5				
NI					15.3				
Total identified					**96.4**				

RI[a] – Retention Index calculated; RI[b] – Retention Index from the NIST webbook database; $RI_{pred.}$ – Retention Index obtained usig QSRR model; GATS5e – Autocorrelation descriptor (Geary autocorrelation - lag 5 / weighted by Sanderson electronegativities); Mv – Constitutional descriptor (Mean atomic van der Waals volumes; scaled on carbon atom); VE1_Dt – Detour matrix descriptor (Coefficient sum of the last eigenvector from detour matrix); MWC9 – Walk counts descriptor (Molecular walk count of order 9 (ln(1+x)); Other[c] – aliphatic hydrocarbons, aliphatic aldehydes and alcohols, aliphatic acids, their esters and aldehydes, aromatic esters with aliphatic acids, alkyl-aromatic alcohols, or aryl esters of aromatic acids; NI[d] – Not Identified compound

***Mass spectrum of NI compounds, m/z (intensity):**

NI-1: 41.05 (43.0), 67.05 (51.0), 69.10 (39.0), 79.00 (39.0), 81.05 (100.0), 91.05 (60.0), 95.00 (44.0), 107.05 (65.0), 109.10 (84.0), 121.10 (86.0)

NI-2: 41.05 (33.0), 55.05 (27.0), 67.05 (70.0), 79.05 (48.0), 81.00 (100.0), 82.05 (23.0), 95.00 (44.0), 96.05 (39.0), 109.00 (43.0), 123.00 (25.0), 152.15 (3.0)

NI-3: 41.10 (20.0), 59.00 (30.0), 67.05 (29.0), 69.05 (24.0), 79.00 (19.0), 81.10 (44.0), 93.10 (19.0), 108.05 (51.0), 109.05 (100.0), 123.10 (14.0), 152.00 (3.0)

NI-4: 43.05 (31.0), 67.05 (23.0), 79.00 (36.0), 80.05 (39.0), 81.05 (24.0), 91.00 (26.0), 93.05 (100.0), 94.05 (23.0), 107.05 (27.0), 121.10 (30.0)

NI-5: 41.05 (62.0), 69.05 (70.0), 77.05 (39.0), 79.05 (54.0), 91.05 (59.0), 93.05 (43.0), 107.05 (41.0), 133.05 (44.0), 134.05 (100.0), 135.05 (53.0), 218.00 (3.0)

NI-6: 41.05 (60.0), 67.05 (56.0), 79.05 (85.0), 91.05 (95.0), 93.05 (100.0), 94.05 (78.0), 105.05 (73.0), 107.00 (67.0), 121.05 (65.0), 159.05 (75.0), 220.10 (47.0)

NI-7: 41.10 (30.0), 55.10 (17.0), 69.05 (100.0), 93.05 (30.0), 94.05 (21.0), 109.10 (23.0), 119.10 (58.0), 137.05 (20.0), 161.10 (17.0), 207.15 (53.0), 222.10 (5.0)

NI-8: 41.05 (30.0), 43.05 (25.0), 79.05 (30.0), 81.05 (25.0), 95.05 (28.0), 105.05 (43.0), 119.05 (100.0), 159.10 (39.0), 161.10 (63.0), 204.15 (31.0), 220.15 (2.0)

NI-9: 79.05 (53.0), 81.05 (59.0), 82.05 (63.0), 91.05 (57.0), 105.05 (63.0), 107.05 (46.0), 119.05 (67.0), 123.05 (100.0), 161.10 (56.0), 177.05 (67.0), 220.15 (13.0)

NI-10: 41.05 (28.0), 55.05 (20.0), 79.05 (23.0), 91.05 (78.0), 93.05 (25.0), 105.05 (28.0), 107.05 (23.0), 119.05 (65.0), 132.05 (100.0), 133.05 (75.0)

NI-11: 67. 10 (21.0), 91.05 (39.0), 121.05 (25.0), 135.05 (58.0), 145.05 (24.0), 147.05 (34.0), 159.05 (49.0), 173.05 (57.0), 201.05 (82.0), 216.10 (100.0)

NI-12: 41.10 (83.0), 79.00 (100.0), 91.05 (93.0), 92.00 (77.0), 93.10 (93.0), 95.05 (81.0), 105.05 (76.0), 107.05 (94.0), 109.05 (87.0), 131.05 (78.0), 220.15 (4.0)

NI-13: 79.05 (30.0), 91.05 (43.0), 93.05 (43.0), 105.05 (39.0), 107.05 (29.0), 109.05 (31.0), 121.05 (42.0), 133.05 (73.0), 159.05 (100.0), 176.10 (100.0), 220.15 (21.0)

NI-14: 67.05 (27.0), 91.05 (44.0), 121.05 (27.0), 135.05 (61.0), 145.05 (25.0), 147.05 (36.0), 159.10 (45.0), 173.10 (59.0), 201.05 (82.0), 216.10 (100.0)

NI-15: 41.05 (46.0), 77.05 (41.0), 81.05 (39.0), 91.05 (84.0), 93.05 (100.0), 105.00 (61.0), 107.05 (46.0), 119.05 (49.0), 133.05 (79.0), 189.05 (58.0), 220.15 (4.0)

NI-16: 41. 00 (89.0), 43.10 (94.0), 55.05 (86.0), 57.05 (100.0), 69.10 (58.0), 82.05 (97.0), 93.05 (88.0), 96.05 (60.0), 107.05 (95.0), 135.05 (84.0)

NI-17: 41.05 (49.0), 43.05 (35.0), 69.05 (55.0), 82.05 (52.0), 91.0 0 (49.0), 93.10 (70.0), 109.05 (35.0) 119.05 (100.0), 121.00 (40.0), 233.10 (35.0), 248.15 (12.0)

NI-18: 41. 00 (51.0), 55.00 (29.0), 69.00 (44.0), 109.05 (45.0), 111.00 (39.0), 125.05 (100.0), 126.05 (27.0), 151.05 (87.0), 153.05 (36.0), 236.15 (34.0)

NI-19: 41.05 (44.0), 43.00 (43.0), 69.05 (49.0), 95.00 (35.0), 108.0 0 (38.0), 109.05 (56.0), 121.05 (39.0) 135.05 (100.0), 136.10 (30.0), 148.05 (32.0), 236.15 (17.0)

NI-20: 41.05 (50.0), 43.05 (38.0), 55.05 (65.0), 67.05 (43.0), 69.05 (50.0), 81.05 (74.0), 93.00 (49.0), 95.05 (100.0), 107.05 (40.0), 109.05 (40.0)

In order to develop a QSRR model for prediction of RIs, PaDel-descriptor software was used. A large set of MDs were calculated, and only the most important descriptors were selected to build the predictive RIs model (12). The four most significant molecular descriptors selected by GA were shown in Table 1. Subsequently, the used MDs were appro-

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priate to foresee the RIs of compounds in *A. millefolium* by multivariate ANN model. Table 2 represents the correlation matrix among these descriptors.

Table 2. Correlations between molecular descriptors

	Mv	VE1_Dt	MWC9
GATS5e	-0.207	-0.007	0.090
	p=0.061	p=0.954	p=0.416
Mv		-0.169	-0.091
		p=0.128	p=0.412
VE1_Dt			0.081
			p=0.465

In order to investigate the nonlinear relationship between RIs of compounds in and MDs selected by GA, ANN modelling tool was used. The neural network MLP 4-8-1 was constructed to predict the retention time of compounds isolated from *A. millefolium* essential oil. The coefficients of determination during the training cycle was 0.862, indicating that this model could be used for prediction of RIs, due to low prediction error and high r^2. The statistical results of the ANN model are shown in Table 3.

Table 3. ANN model summary (performance and errors), for training, testing and validation cycles

Net. name	Performance			Error			Train. algor.	Error funct.	Hidden activat.	Output activat.
	Train.	Test.	Valid.	Train.	Test.	Valid.				
MLP 4-8-1	0.862	0.884	0.973	14496.458	32524.903	6374.756	BFGS 72	SOS	Logistic	Identity

*Performance term represent the coefficients of determination, while error terms indicate a lack of data for the ANN model. ANN cycles: Train. – training, Test. – testing, Valid. – validation, algor. –algorythm, funct. – function, activat. – activation.

The predicted RIs are presented in Fig. 1, confirming the good quality of the constructed ANN, by showing the relationship between the predicted and experimental RIs values. Graphical comparison between: experimentally obtained retention indices of *A. millefolium* essential oil essential oils composition (RI^a), and the retention time indices predicted by the four ANN models ($RI_{pred.}$) were presented in Fig. 2. The obtained results presented in Fig. 1 and Fig. 2 show the good reliability of the ANN models for predicting the RIs of compounds in *A. millefolium* essential oil obtained by GC-MS analysis. The influence of four most important input variables, identified using genetic algorithm on RIs was studied. According to the Fig. 3, MWC9 was the most important MD for chemical compounds in *A. millefolium* essential oil. The positive influence was observed for GATS5e descriptor, while the two negative influential MDs with almost equally importance were: Mv and VE1_Dt.

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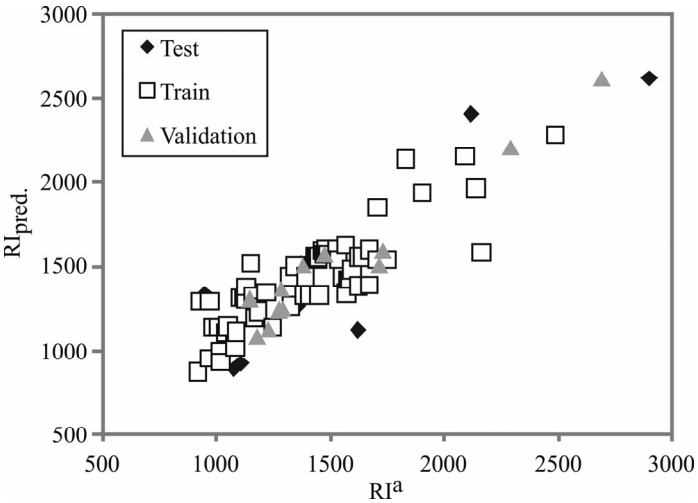

Figure 1. Retention time indices of the *A. millefolium* essential oil composition, from: experimentally obtained GC-MS data (RI^a) and predicted by the ANN ($RI_{pred.}$).

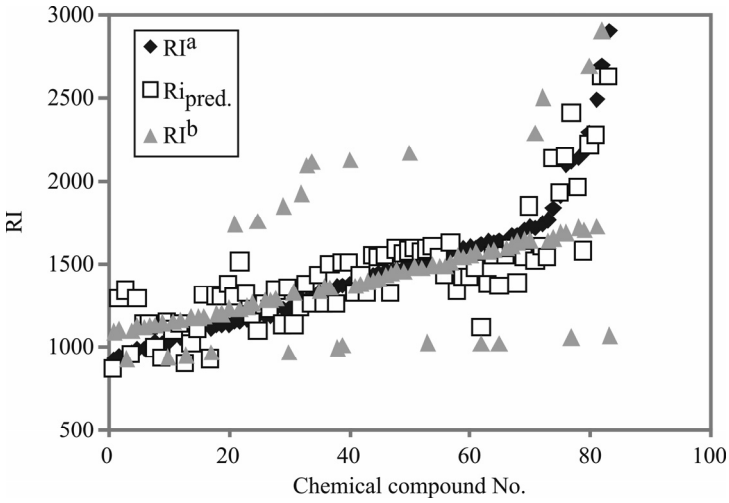

Figure 2. Comparison of experimentally obtained RIs with ANN predicted values

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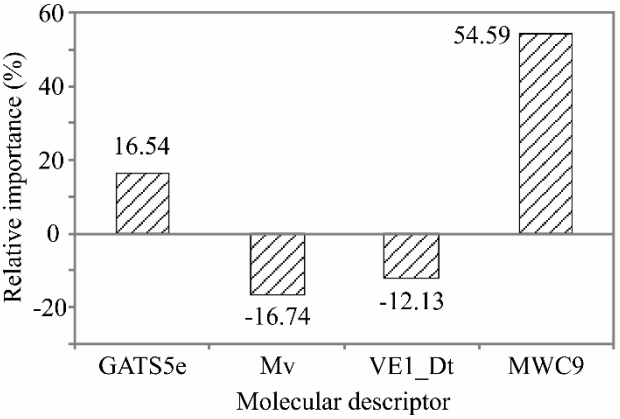

Figure 3. The relative importance of the molecular descriptors on RI, determined using Yoon interpretation method

Investigations of *A. millefolium* composition from different countries showed that the quantitatively most important components of the oil were chamazulene, *β*-pinene, sabinene, bornyl acetate, *β*-caryophyllene, *E*-nerolidol, 1,8-cineole and germacrene D (15). The most frequently identified compound among the monoterpenes was 1,8-cineole, found in almost every essential oil, followed by compounds with bornane skeleton such as camphor and borneol (16). The basic chromosome number of *Achillea* species is x=9, but the diversity in chromosome numbers and ploidy levels occurs frequently in this genus. Consequently, there are diploid, tetraploid, hexaploid and octaploid accessions (15; 17). However, diploid and tetraploid accessions contain chamazulene and their essential oil is blue, while the accessions with high percentage of oxygenated monoterpenes and absence of azulene in the essential oil are characterized by being pale yellow (hexaploid and octaploid) (15; 18). Furthermore, population developed by hybridization and polyploidy exhibits great variation and ecological divergence (19). The color of essential oil of *A. millefolium* from Rtanj Mt. indicated that it could be hexaploid or octaploid accession. However, hexaploid accessions of *A. millefolium* aggregate have the widest range of spreading, usually as a weed throughout Europe and Asia (17). Furthermore, oxygenated monoterpenes as the dominant class (28.1%) with compounds such as camphor, terpinen-4-ol and 1,8-cineole could be eco-geographical characters of accessions from this specific mountain. Further cytogenetic investigation need to be done to confirm this.

CONCLUSION

In the essential oil from the *A. millefolium sensu lato* collected in Rtanj Mt. 104 compounds were detected, and the most abundant were camphor, caryophyllene oxide, terpinen-4-ol and 1,8-cineole. The results showed that the selected four molecular descriptors were adequate in predicting the retention indices of the observed chemical compounds. The coefficients of determination for training cycle were 0.862 (for compounds found in *A. millefolium* essential oil.

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REFERENCES

1. Josifović, M. Flora SR Srbije. Vol 7. Srpska akademija nauke i umetnosti, Beograd, Serbia, **1975**.
2. Pljevljakusic, D.; Ristic, M.; Savikin, K. Screening of yarrow (*Achillea millefolium* Agg.) populations in Serbia for yield components and essential oil composition. *Lekovite Sirovine*. **2017**, *37*, 25-32.
3. Orth, M.; Czygan, F.C.; Dedkov, V. Variation in essential oil composition and chiral monoterpenes of *Achillea millefolium* S.L. from Kaliningrad. *Journal of Essential Oil Research*. **1999**, *11*, 681-687.
4. Tucakov, J. Lečenje biljem: fitoterapija. Rad, Beograd, Srbija, **2006**.
5. Hashempur, M.H.; Khademi, F.; Rahmanifard, M.; Zarshenas, M. An evidence-based study on medicinal plants for hemorrhoids in Medieval Persia. *Journal of Evidence-Based Complementary and Alternative Medicine*. **2017**, *22*, 969-981.
6. Nirmala, S.; Karthiyayini, T. Wound healing activity on the leaves of *Achillea millefolium* L. by excision, incision, and dead space model on adult Wistar albino rats. *International Research Journal of Pharmacy*. **2011**, *2*, 240-245.
7. Mohamed, D.; Hanfy, E.; Fouda, K. Evaluation of antioxidant, anti-inflammatory and anti-arthritic activities of yarrow (*Achillea millefolium*). *Journal of Biological Sciences*. **2018**, *18*, 317-328.
8. Mazandarani, M.; Mirdeilami, S.Z.; Pessarakli, M. Essential oil composition and antibacterial activity of *Achillea millefolium* L. from different regions in North east of Iran. *Journal of Medicinal Plants Research*. **2013**, *7*, 1063-1069.
9. Aćimović, M.; Zorić, M.; Zheljazkov, V.D.; Pezo L.; Čabarkapa, I.; Stanković Jeremić J.; Cvetković, M. Chemical characterization and antibacterial activity of essential oil of medicinal plants from Eastern Serbia. Molecules. **2020**, *25*, 5482; doi:10.3390/molecules25225482
10. Acar, M.B.; İbiş, E.K.; Şimşek, A.; Vural, C.; Tez, C.; Özcan, S. Evaluation of *Achillea millefolium* essential oil compounds and biological effects on cervix cancer HeLa cell line. *The EuroBiotech Journal*. **2020**, *4*, 17-24.
11. Aćimović, M.; Pezo, L.; Stanković Jeremić, J.; Cvetković, M.; Rat, M.; Čabarkapa, I.; Tešević, V. QSRR model for predicting retention indices of geraniol chemotype of *Thymus serpyllum* essential oil. *Journal of Essential Oil Bearing Plants*. **2020**, *23*, 464-473.
12. Aćimović, M.; Pezo, L.; Tešević, V.; Čabarkapa, I.; Todosijević, M. QSRR Model for predicting retention indices of *Satureja kitaibelii* Wierzb. ex Heuff. essential oil composition. *Industrial Crops and Products*. **2020**, *154*, 112752.
13. Yap, C.W. PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints. *Journal of Computational Chemistry*. **2011**, *32*, 1446-1474.
14. Yoon, Y.; Swales, G.; Margavio, T.M. A comparison of discriminant analysis versus artificial neural networks. *Journal of the Operational Research Society*. **2017**, *44*, 51-60.
15. Raal, A.; Orav, A.; Arak, E. Essential oil content and composition in commercial *Achillea millefolium* L. herbs from different countries. *Journal of Essential Oil Bearing Plants*. **2012**, *15*, 22-31.
16. Turkmenoglu, F.P.; Agar, O.T.; Akaydin, G.; Hayran, M.; Demirci, B. Characterization of volatile compounds of eleven *Achillea* species from Turkey and biological activities of essential oil and methanol extract of *A. hamzaoglui* Arabaci & Budak. *Molecules*. **2015**, *20*, 114432-11458.

17. Guo, Y.P.; Saukel, J.; Ehrendorfer, F. AFLP trees versus scatterplots: evolution and phylogeography of the polyploidy complex *Achillea millefolium* agg. (Asteraceae). *Taxon*. **2008**, *57*, 153-169.
18. Bozin, B.; Mimica-Dukic, N.; Bogavac, M.; Suvajdzic, Lj.; Simin, N.; Samojlik, I.; Couladis, M. Chemical composition, antioxidant and antibacterial properties of *Achillea collina* Becker ex Heimerl s.l. and *A. pannonica* Scheele essential oils. *Molecules*. **2008**, *13*, 2058-2068.
19. Ma, J.X.; Li, Y.N.; Vogl, C.; Ehrendorfer, F.; Guo, Y.P. Allopolyploid specification and ongoing backcrossing between diploid progenitor and tetraploid progeny lineages in the *Achillea millefolium* species complex: analyses of single-copy nuclear genes and genomic AFLP. *BMC Evolutionary Biology*. **2010**, *10*, 100.