Chemical Composition of the Essential Oil from *Nepeta macrosiphon Boiss.* Growing Wild in Iran by Different Extraction Methods and Studies on the Quantitative Relationship Between the Retention Indices of Essential Oils and their Molecular Structures

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Hydrodistillation, solvent free microwave extraction and solid phase microextraction methods has been applied to extraction of essential oil from *Nepeta macrosiphon* growing in Iran. Spathulenol (28.8, 32.28 and 7.68) and β-caryophyllene (9.6,5.83 and 15.19) were the main compounds in the essential oil, respectively. High amount of sesquiterpenes and low quantity of hydrocarbon monoterpenes were identified in the essential oils. Then a simple, strong, descriptive and interpretable model, based on a quantitative structure-retention relationship is developed using stepwise multiple linear regression (SW-MLR) approach for prediction of the retention index (RI) of *Nepeta macrosiphon* essential oil. A model with low prediction error (2.071 %) and good coefficient of determination (0.982) was obtained. This model was used for the prediction of the RI values of some essential oil components which were not used in the modeling procedure.

Key Words: *Nepeta macrosiphon*, Spathulenol, Quantitative structure-retention relationship, Stepwise multiple linear regression.

INTRODUCTION

Essential oils are isolated from different sections of plants such as flowers, seeds, leaves, stems and roots. Essential oil are applied extensively in the perfume, cosmetic, foods, beverages and confectioneries and as ingredients of disinfectants and insecticides[1]. Essential oil can be separated using some isolation methods, such as hydrodistillation (HD), steam distillation (SD), solid phase micro extraction (SPME), ultrasonic extraction (US), microwave assisted distillation (MAD) and solvent free microwave extraction (SFME). Hydrodistillation has been typical method to extract the essential oils from herbal plants. Nevertheless, in order to decrease operation time, costs and solvent depletion, to obtain higher yields and purity and also to improve the quality of the extracts, new methods namely, microwave-assisted extraction, supercritical fluid extraction and solvent free microwave extraction have been utilized[2].

Solid phase micro extraction is sample preparation methods in this method extraction and sample preparation are carried out into one step. Solid phase micro extraction utilizes a fused silica fiber coated with a liquid (polymer) or a solid (sorbent).

The coated fiber is submerged into an aqueous solution sample or the headspace above the sample. Analytes are extracted by fiber after extraction, analytes are desorbed from the coated fiber to a chromatography column. Solid phase micro extraction has some advantages such as solvent less,fast sampling, low cost and sensitivity[3].

Microwave extraction is research field in modern chemistry. Microwave-assisted extraction is appropriate alternative to conventional techniques. The basic advantages of using microwave energy are decrease of extraction time and cost, faster energy transfer and deletion of process steps. Solvent free microwave extraction is carried out at atmospheric pressure and no need to add any water and solvent. In this method, herbal plant is put in microwave reactor the internal heating of *in situ* water within fresh plant swells it and result in the gland and oleiferous receptacles fracture. Therefore essential oil is released and evaporated by the *in situ* water. The distillate condensed by the external cooling system[4,5].

The genus *Nepeta* (Lamiaceae) with the common Persian name of pune-say comprises about 280 species in the world and 67 species that are found all over of Iran[6]. Some species are applied in folk medicine as a fortifier, disinfectant, bacteriostatic

and treating eczema type disorders[7,8]. *Nepeta macrosiphon* Boiss distributed in various rocky western areas of Iran[7]. The Persian names of the plant are "punesay-e-sisakhti" and "punesay-elulehboland"[6]. Chemical composition of the essential oil of *Nepeta macrosiphon* has been studided[10,11]. In this work, analysis of the essential oil compounds of *Nepeta macrosiphon* were performed by GC and GC-MS equipment. The essential oil was achieved with hydro distillation (HD), solid phase micro extraction (SPME) and solvent free microwave extraction (SFME) methods.

Nowadays much interest is devoted to the prediction of physicochemical properties of molecules, such as their biological activity, chemical property, or their retention on chromatographic systems, *etc*. This is usually accomplished by implementing so-called quantitative structure-property relationship (QSPR) models, which relate the property of interest, with a set of molecular descriptors. Quantitative structure-retention relationships (QSRR) have also been used to obtain simple models to explain and predict the chromatographic behaviour of various classes of compounds[12-18]. Quantitative structure-retention relationships are statistical models which quantify the relationship between the structure of a molecule and its chromatographic retention index, enabling prediction of the retention indices of novel compounds.

Application of these techniques usually requires selection of variables to build well-fitting models. In this work we used the stepwise method for variable selection in multiple linear regression.

The aim of this work is analysis of the essential oil compounds of *Nepeta macrosiphon* and to search for an efficient method to build an accurate quantitative relationship between the molecular structure and the retention indices of the *Nepeta macrosiphon* essential oils by stepwise-multiple linear regression.

EXPERIMENTAL

Plant material: *Nepeta macrosiphon* was collected in May 2010, from the Dena Mountain in Kohgiluyeh and Boyerahmad Province.

Gas chromatography: Analytical GC was carried out on a Shimadzu 15A gas chromatography equipped with a split/ splitless injector (250 °C) and a flame ionization detector (250 °C). DB-5 capillary column (30 m × 0.25 mm, film thickness 0.32 μm) and type of carrier gas was N_2 (1 mL/min). The column temperature was held at 60 °C for 3 min and then heated to 250 °C with a 6 °C/min rate and held constant at 250 °C for 5 min.

Gas chromatography-mass spectrometry: GC-MS analyses were accomplished by Hewlett-Packard (HP-6890/ 5973) GC-MC system coupled with an HP-5MS column (30 m × 0.25 mm, film thickness 0.32 μm). The column temperature was as like as GC condition. Helium was used as carrier gas (1 mL/min) beside ionization energy in MS was 70 eV, mass range 40-300 amu and scan time was 1 s.

Isolation methods

Hydrodistillation: Dried aerial part of *Nepeta macrosiphon* (100 g) were submitted to hydro distillation with a Clevenger-type apparatus for 4 h and the oils were dried under anhydrous sodium sulphate and kept in 4 °C until analyzed.

Solvent free microwave extraction (SFME): A Milestone Microsynth microwave apparatus, 2450 MHz and ACTE0 sensor was applied. The maximum power was 1000 W. The air-dried of *Nepeta macrosiphon* (35 g) was immersed in 25 mL distilled water for 1 h due to hydrate of the plant. The moistened plant was heated by an optimize power 800 w and time 25 min. The extracted oils were dried with anhydrous sodium sulphate and stored in 4 °C until analyzed.

Head space solid phase micro extraction (HS-SPME): 1.5 g of different parts (flower, leave and stem) of powdered sample was placed in 20 mL SPME vial sealed with PTFE septum caps from supelco (Bellefonte, USA). The vial was heated at 70 °C for 15 min then a 65 μm polydimethylsiloxne-divinylbenzene (PDMS-DVB) fiber (supelco, USA) was subjected to head space of sample for 15 min. Analytes desorption was performed at 250 °C for 3 min in a splitless GC injector.

Components identification: Identification of components was performed by comparison of their MS spectra and GC retention indices with those of authentic references[19] and Wiley 257 mass spectra database. The retention indices were figured out using homologous series of normal alkanes.

Molecular descriptors: Molecular descriptors are defined as numerical characteristics associated with chemical structures. The molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number applied to correlate physical properties.

The Dragon software was used to calculate the descriptors in this research and a total of 1481 molecular descriptors, from 18 different types of theoretical descriptor, were calculated for each molecule. Since the values of many descriptors are related to the bonds length and bonds angles *etc*., the chemical structure of every molecule must be optimized before calculating its molecular descriptors. For this reason, chemical structure of the 54 studied molecules were drawn with the Hyperchem software and saved with the HIN extension. To optimize the geometry of these molecules, the AM1 geometrical optimization was applied. After optimizing the chemical structures of all compounds, the molecular descriptors were calculated using Dragon. A wide variety of descriptors have been reported in the literature, having been used in the QSRR analysis[20-25].

RESULTS AND DISCUSSION

The percentage composition of essential oil from *Nepeta macrosiphon* with three isolation methods is shown in Table-1.

Spathulenol (28.8, 32.28 and 7.68) and β-caryophyllene (9.6, 5.83 and 15.19) were the main compounds in the essential oil of *Nepeta macrosiphon* that achieved by hydrodistillation, solvent free microwave extraction and headspace-solid phase micro extraction, respectively.

The oils were obtained by these methods has high amount of sesquiterpenes and low quantity of hydrocarbon monoterpenes. Comparing these results with previous studies on oil of *Nepeta macrosiphon* demonstrated that they were also predominated by sesquiterpenes.

Fig. 1 showed that the essential oil obtained by SFME method has higher quantity of oxygenated compounds and

TABLE-1
CHEMICALCOMPOSISION OF *Nepeta macrosiphon*
BY VARIOUS METHODS

| No.	Component name	Kovats index	Content (%)		
			HD	SFME	HS-SPME
1	α-Thujene	930	0.4	–	3.32
2	α-Pinene	939	0.9	–	7.37
3	Sabinene	975	0.4	1.18	2.31
4	β-Pinene	979	0.4	–	2.01
5	α-Phellandrene	1003	0.2	–	0.38
6	α-Terpinene	1017	0.5	–	–
7	β-Phellandrene	1030	–	–	4.54
8	γ-Terpinene	1060	0.9	–	–
9	Sabinane hydrate (*cis*)	1070	0.3	1.05	0.18
10	α-Terpinolene	1089	0.4	–	–
11	Linalool	1097	5.6	5.70	3.44
12	Sabinane hydrate(trans)	1098)	–	0.36	–
13	Menthe -2-en-1-Ol(*cispara*)	1122	–	1.26	–
14	Terpinen (1)	1134	0.3	–	–
15	Trans verbenol	1145	0.2	–	–
16	Terpinen-4-ol	1177	1.9	–	–
17	α-Terpineol	1189	0.9	0.81	–
18	Geraniol	1253	0.5	–	–
19	Δ-Elemene	1338	–	1.64	8.05
20	α-Cubebene	1351	0.3	–	–
21	β-Bourbonene	1388	0.3	0.2	0.96
22	β-Elemene	1391	0.4	–	–
23	α-Gurjunene	1410	1.06	0.73	3.91
24	β-Caryophyllene	1419	9.6	5.83	15.19
25	β-Copaene	1432	–	–	0.19
26	β-Gurjunene	1434	0.1	–	2.68
27	Aromadendrene	1441	0.8	0.56	–
28	α-Humulene	1455	0.6	0.59	1.86
29	Alloaromadendrene	1460	1.8	–	1.44
30	γ-Gurjunene	1460	0.3	–	–
31	Germacron-D	1485	0.3	1.24	2.2
32	Phenyl ethyl 2-methyl Butanoate	1487	–	0.71	0.23
33	β-Selinene	1490	–	–	0.77
34	β-*Cis*guaiene	1493	–	–	1.28
35	Muurola 4(14),5 Diene(*trans*)	1494	–	0.19	–
36	Bicyclogermacrene	1500	10.1	4.79	6.48
37	E,E-α-Farnesene	1506	0.4	–	–
38	γ-Cadinene	1514	2.5	2.47	4.16
39	Δ-Cadinene	1523	2.6	–	0.3
40	α-Cadinene	1539	0.4	–	–
41	1-Hydroxy-1,7-dimethyl-4-isopropyl-2,4-cyclodeca diene	1553	2.0	–	3.33
42	Germacrene B	1561	–	4.04	–
43	Germacrene D-4-ol	1576	–	2.42	1.19
44	Spathulenol	1578	28.8	32.28	7.68
45	Caryophyllene oxide	1583	1.5	–	1.26
46	Viridiflorol	1593	–	2.08	–
47	Cubenol(1,10-di-epi)	1619		3.12	1.31
48	Eudesmol(10-epi-γ)	1624	0.6	0.85	–
49	Cadinol(epi-α)	1640	–	13.40	6.15
50	Selina 3,11-dien-6-α-ol	1644	–	2.35	–
51	Cedr-8(15)-en-10-ol	1652	–	–	0.78
52	α-Cadinol	1654	13.6	–	–
53	Caryophyllene(14-hydroxy-9-epi-E)	1670	–	1.63	–
54	Benzyl benzoate	1760	0.3	0.33	–
	Total (%)		91.86	91.81	94.95
	Monoterpene (%)		13.8	10.36	23.55
	Sesquiterpene (%)		77.76	80.41	71.17
	Oxygenated compound (%)		55.9	64.89	25.32
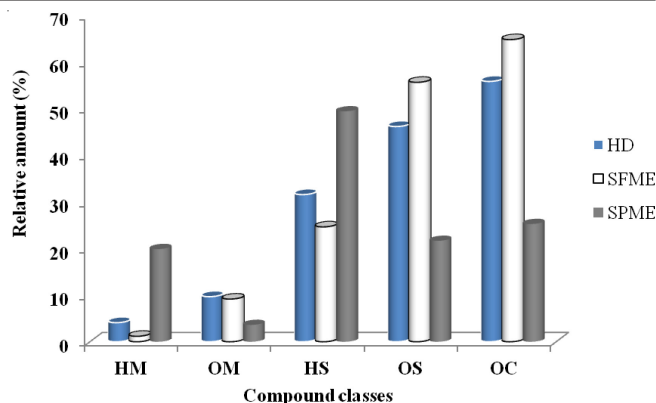
Fig. 1.   Comparison of relative amount of different compounds classes by various methods

lower amount of monoterpenes hydrocarbons than the essential oil extracted by HD method. Solvent free microwave extraction uses rapid heating of polar solvent (water), smaller quantity of water, time and energy consuming compared with traditional HD method which leads to reduction in decomposition of oxygenated compounds by thermal and hydrolytic effects[26].

Theoretical results: A stepwise multiple linear regression procedure was used for variable selection. This method has been used for variable selection or model development in variety systems[27,28]. For regression analysis, data set was separated into two groups: training and prediction sets. The molecules included in these sets were selected randomly. The training set, consisted of 43 molecules, was used for the model generation using the SPSS software package. The prediction set, consisted of 11 molecules, was used to evaluate the generated model. It is clear that many multiple linear regression models will result using stepwise multiple regression procedure; among them we have to choose the best one. It is common to consider four statistical parameters for this purpose. These parameters are the number of descriptors, coefficient of determination (R^2) for training and prediction sets, standard error (SE) for training and prediction sets and F statistic. A reliable multiple linear regression model is one that has high R^2 and F values, low SE and least number of descriptors. In addition to these, the model should have a high predictive ability. Consequently, among different models, the best model was chosen, whose specifications are presented in Table-2. It is obvious that as the number of descriptors increase the R^2 will increase. Fig. 2 shows the effect of increasing the number of descriptors on R^2 values. It can be seen from this figure that increasing the number of parameters only up to seven has a large influence on improving correlation. Therefore, we have chosen seven descriptors as optimum number of parameters. The descriptors appearing in this model and definitions are given in Table-2. Dragon software can easily calculate these descriptors and their equations are not given here for the sake of brevity[1]. As it can be seen from the correlation matrix (Table-3) there is no significant correlation between the selected descriptors.

The data set and the corresponding experimental and predicted RI values of all the molecules studied in this work are summarized in Table-4. Fig. 3 shows a plot of values predicted by the SW-MLR against experimental values of the retention indices of the training and prediction sets. The residuals

TABLE-2
SELECTED DESCRIPTORS OF MULTIPLE LINEAR REGRESSION

Descriptor	Type of descriptor	Notation	Coefficient
Modified Randic chi-1 index	Topological	XMOD	29.004
Moran autocorrelation-lag1/weighted by atomic Sanderson electronegativities	2D autocorrelations	MATS1e	-953.683
Mean topological charge index of order1	Galvez topol.charge indices	JGI1	-454.513
The symbol C-002 corresponds to: CH_2R_2	Atom-centred fragments	C-002	23.307
H autocorrelation of lag 7/weighted by atomic masses	GETAWAY	H7m	-1402.278
Distance/detour ring index of order 6	Topological	D/Dr06	0.589
2nd component accessibility directional WHIM index/ weighted by atomic masses	WHIM	E2m	348.373
Constant	–	–	231.432

$R^2_{calibration} = 0.991$, $R^2_{prediction} = 0.982$, $Q^2_{LOO} = 0.988$, $Q^2_{LGO} = 0.986$, REP (%) = 2.07, $F_{train} = 570.62$, $F_{test} = 24.85$, RMSEP = 29.015.

TABLE-3
CORRELATION MATRIX FOR THE FOUR SELECTED DESCRIPTORS

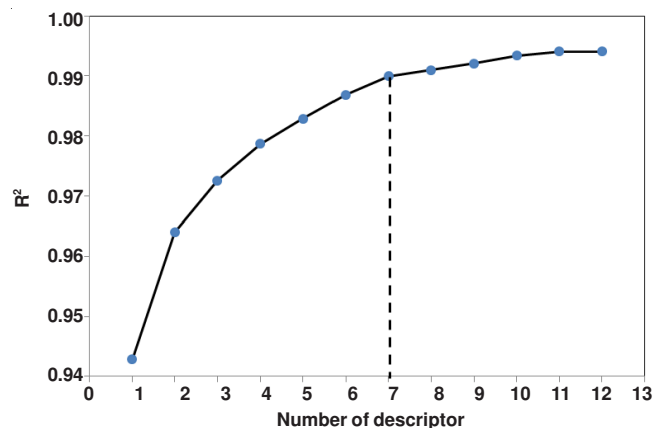|	MATS1e	JGI1	C-002	H7m	D/Dr06	E2m	MATS1e
MATS1e	1	–	–	–	–	–	–
JGI1	0.115	1	–	–	–	–	–
C-002	-0.365	-0.419	1	–	–	–	–
H7m	0.559	0.189	0.021	1	–	–	–
D/Dr06	0.492	-0.071	-0.187	0.191	1	–	–
E2m	0.048	0.062	-0.137	-0.184	0.129	1	–
MATS1e	0.654	0.058	-0.283	0.333	0.231	-0.112	1

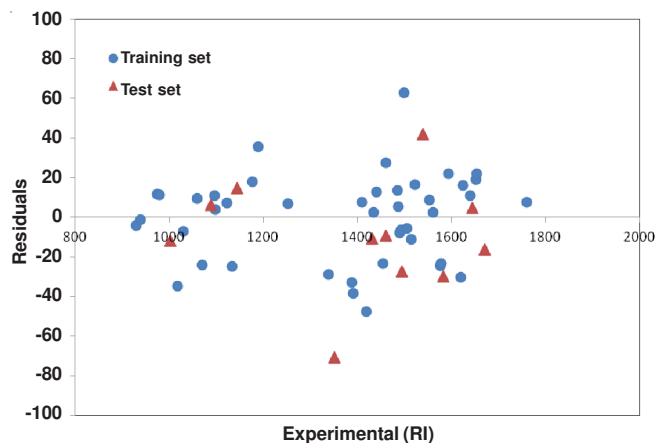Fig. 2. Influence of number of descriptors on R^2 of MLR model

Fig. 4. Plot of the residuals against the experimental values of the retention indices
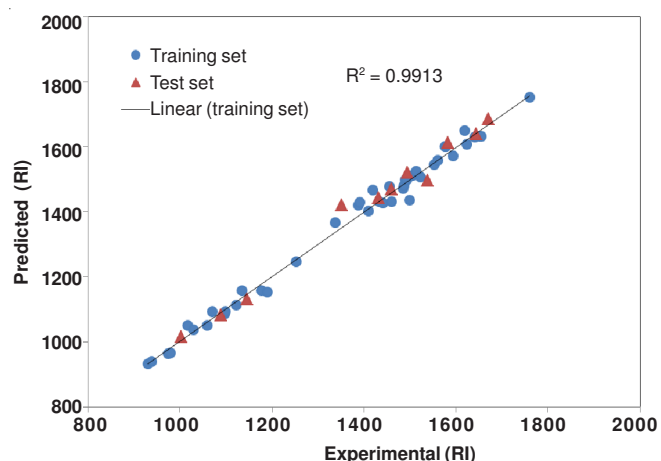

Fig. 3. Predicted RI values by the MLR modeling *vs.* the experimental retention index (RI) values

experimental RI-predicted RI) *versus* experimental RI value, obtained by the SW-MLR modeling, shown in Fig. 4. The distribution of the residuals on both sides of the zero line indicates there is no systematic error in the SW-MLR model.

Statistical parameters: For evaluation of the predictive power of the generated MLR, the optimized model was applied for prediction of RI values of test compounds in the prediction set, which were not used in the optimization procedure. For the constructed models, two general statistical parameters were selected to evaluate the prediction ability of the model for RI. For this case, the predicted RI of each sample in prediction step was compared with the experimental RI.

Root mean square error of prediction (RMSEP) is a measurement of the average difference between predicted and experimental values, at the prediction stage. RMSEP can be interpreted as the average prediction error, expressed in the same units as the original response values. The RMSEP was obtained by the following formula:

$$RMSEP = \left[\frac{1}{2} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2 \right]^{0.5} \qquad (1)$$

The second statistical parameter was relative error of prediction (REP) that shows the predictive ability of each component and is calculated as

TABLE-4
DATA SET AND THE CORRESPONDING OBSERVED AND
PREDICTED RETENTION INDEX (RI) VALUES BY
SW-MLR FOR THE TRAINING AND TEST SET

No.	Compound	RI (exp)[a]	RI (SW-MLR)[b]	E (%)[c]
		Training set		
1	α-Thujene	930	934.17	0.45
2	α-Pinene	939	939.98	0.10
3	Sabinene	975	963.40	-1.19
4	β-Pinene	979	967.47	-1.18
5	α-Terpipinene	1017	1051.76	3.42
6	β-Phellandrene	1030	1037.13	0.69
7	γ-Terpinene	1060	1050.37	-0.91
8	*cis*-Sabinene hydrate	1070	1093.84	2.23
9	Linalool	1097	1085.95	-1.01
10	*trans*-Sabinene hydrate	1098	1093.84	-0.38
11	Menthe-2-en-1-ol	1122	1114.56	-0.66
12	Terpinene -1	1134	1158.58	2.17
13	Terpinene-4-ol	1177	1159.01	-1.53
14	α-Terpineol	1189	1153.34	-3.00
15	Geraniol	1253	1246.10	-0.55
16	δ-Elemene	1338	1366.67	2.14
17	β-Bourbonene	1388	1420.65	2.35
18	β-Elemene	1391	1429.25	2.75
19	α-Gurjunene	1410	1402.35	-0.54
20	β-Caryophyllene	1419	1466.50	3.35
21	β-Gurjunene	1434	1431.43	-0.18
22	Aromadendrene	1441	1428.23	-0.89
23	α-Humulene	1455	1478.09	1.59
24	Alloaromadendrene	1460	1432.41	-1.89
25	Germacron-D	1485	1471.25	-0.93
26	Phenylethyl2-methylbutanoate	1487	1481.64	-0.36
27	β-Selinene	1490	1497.76	0.52
28	β-*cis*-Guaiene	1493	1499.35	0.43
29	Bicyclogermacrene	1500	1437.28	-4.18
30	E,E-α-Farnesene	1506	1511.66	0.38
31	γ-Cadinene	1514	1524.91	0.72
32	δ-Cadinene	1523	1506.41	-1.09
33	1-Hydroxy-1,7-dimethyl-4-isopropyl-2,4-cyclodecadiene	1553	1544.26	-0.56
34	Germacrene B	1561	1558.39	-0.17
35	Germacrene D-4-ol	1576	1600.41	1.55
36	Spathulenol	1578	1601.40	1.48
37	Viridiflorol	1593	1571.04	-1.38
38	Cubenol(1,10-di-epi)	1619	1649.25	1.87
39	γ-Eudesmol(10-epi)	1624	1607.81	-1.00
40	α-Cadinol(epi)	1640	1628.88	-0.68
41	Cedr-8(15)-en-10-ol	1652	1633.04	-1.15
42	α-Cadinl	1654	1632.00	-1.33
43	Benzyl benzoate	1760	1752.18	-0.44
		Test set		
1	α-Phellandrene	1003	1014.87	1.18
2	–	1089	1082.74	-0.58
3	*trans*-Verbenol	1145	1130.49	-1.27
4	α-Cubebene	1351	1421.57	5.22
5	β-Copaene	1432	1442.84	0.76
6	γ-Gurjunene	1460	1469.41	0.64
7	Muurola 4(14),5dien(trans)	1494	1521.38	1.83
8	Alphcadinene	1539	1497.07	-2.72
9	Caryophyllene oxide	1583	1612.94	1.89
10	Selina 3,11-dien-6-alpha-ol	1644	1639.24	-0.29
11	Caryophyllene (14-hydroxy-9-epi-E)	1670	1686.06	0.96

[a]Experimental retention index. [b]Stepwise multiple linear regression retention index. [c]Relative error.

$$REP\ (\%) = \frac{100}{\bar{y}} \left[\frac{1}{n} \sum_{i=1}^{n} (\hat{y}_i - y_i)^2 \right]^{0.5} \quad (2)$$

where y_i is the experimental RI of the essential oil in the sample i, $\hat{y}_i$ represents the predicted RI of the essential oil in the sample i, $\hat{y}$, is the mean of experimental RI in the prediction set and n is the total number of samples used in the prediction set. The statistical parameters calculated for the SW-MLR model are listed in under Table-2.

Also the model obtained was validated using leave-one-out (LOO) and leave-group-out (LGO) cross-validation process. For LOO cross-validation, a data point is removed from the set and the model is recalculated. The predicted property for that point is then compared with its actual value. This is repeated until each data point is omitted once. For LGO, 20 % of the data points are removed from the dataset and the model is refitted, the predicted values for those points are then compared with its experimental values. Again, this is repeated until each data point has been omitted once. The cross-validation correlation coefficient (Q^2) is 0.986 for LGO and 0.988 for LOO. This confirms that the obtained regression model has a good internal and external-predictive power.

Conclusion

In this study, the essential oil of *Nepeta macrosiphon* was extracted by hydro distillation (HD), solvent free microwave extraction (SFME) and solid phase micro extraction (SPME) methods. Fifty four compounds were identified by mass spectrometry. The essential oil obtained by SFME method has higher content of oxygenated compounds and smaller amount of monoterpenes hydrocarbons than the essential oil extracted by HD method. The oxygenated compounds are very odoriferous and more important than monoterpenes hydrocarbons. Compared to many extraction methods SFME is simple, fast, green and solvent free for extraction of essential oil from material plants. Simple QSRR model was presented for prediction RI of the essential oils. This model is a multivariate linear model, which has seven variables (molecular descriptors). These seven molecular descriptors were selected using SW-MLR technique. These variables are calculated based on the chemical structure molecules. The QSRR model with simply calculated molecular descriptors could be employed to estimate the retention index for new compounds, even in the absence of the standard candidates.

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