

Article

Chemical Composition, Chemometric Analysis, and Sensory Profile of *Santolina chamaecyparissus* L. (Asteraceae) Essential Oil: Insights from a Case Study in Serbia and Literature-Based Review

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Abstract: The flowers of *Santolina chamaecyparissus* have a distinct aroma and taste, with a wide range of applications in medicine, food, and packaging. Its essential oil offers numerous health benefits, including antioxidant, hepatoprotective, anticancer, antidiabetic, spasmolytic, anti-inflammatory, immunomodulatory, antimicrobial, and antiparasitic properties. Additionally, it is used as a flavoring agent in food and beverages and as a natural preservative in edible coatings for food packaging. This study investigates the chemical composition and sensory properties of the *S. chamaecyparissus* essential oil from Serbia, obtained via hydrodistillation, and includes a literature-based analysis of the existing profiles. Gas Chromatography–Mass Spectrometry (GC–MS) was employed for identifying the essential oil composition, while chemometric techniques like the genetic algorithm (GA), quantitative structure–retention relationship (QSRR) analysis, artificial neural network (ANN), and molecular descriptors were applied to ensure accurate and reliable results for authenticating the oil. Among the 47 identified compounds, oxygenated monoterpenes, especially artemisia ketone (36.11%), and oxygenated sesquiterpenes, notably vulgarone B (22.13%), were the primary constituents. Chemometric analysis proved effective in predicting the oil's composition, and sensory evaluation revealed a herbal aroma with earthy, woody, and camphoraceous notes. A literature review highlighted the variability in oil composition due to geographical, environmental, and extraction factors, underscoring its chemical diversity, bioactivity, and potential applications.

Keywords: volatile compounds; artemisia ketone; vulgarone B; chemotypes; cluster analysis; chemometrics



Academic Editor: Katelynn A. Perrault

Received: 27 March 2025

Revised: 23 April 2025

Accepted: 29 April 2025

Published: 2 May 2025

Citation: Lončar, B.; Cvetković, M.; Rat, M.; Jeremić, J.S.; Filipović, J.; Pezo, L.; Aćimović, M. Chemical Composition, Chemometric Analysis, and Sensory Profile of *Santolina chamaecyparissus* L. (Asteraceae) Essential Oil: Insights from a Case Study in Serbia and Literature-Based Review. *Separations* **2025**, *12*, 115. <https://doi.org/10.3390/separations12050115>

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1. Introduction

Santolina chamaecyparissus L. (Asteraceae) is a Mediterranean plant that has been used in the traditional medicine of this region since ancient times [1]. Its Latin name is derived from the words ‘*santo*’, meaning saint, referring to the medicinal properties of the herb, ‘*chamai*’, meaning low-growing, on the ground, creeping, and ‘*kyparissos*’, meaning like cypress, referring to the leaves resembling those of the cypress [2,3]. However, the common name “cotton lavender” is somewhat misleading, as the plant has no botanical connection to either lavender or cotton.

S. chamaecyparissus grows as a small perennial shrub with flowering and non-flowering stems. The entire plant, including leaves, stem, and bracts, is covered with dense simple hairs. The non-flowering stems are clearly more tomentose than the flowering stems, which are slightly pubescent [4]. The leaves are narrow, alternate, compact, densely pectinate-dentate to pinnately dissected, with 10 to 20 segments [5]. The head-like inflorescences are globular, 1–2 cm in diameter, and are composed of yellow tubular flowers [6].

The secondary metabolites from this plant included essential oil and phenolic compounds (phenolic acids, flavonoids, and coumarins) [1,7,8]. Numerous studies have confirmed its medicinal potential, as it is a plant rich in antioxidants [2,7,9–11]. It is commonly used for its hepatoprotective [12,13], anticancer [14–18], and antidiabetic properties [7,15], as well as for its spasmolytic, anti-inflammatory and immunomodulatory effects [19–23]. Its antimicrobial properties have also been reported against a wide range of pathogens [24–26], as well as notable antiparasitic activity [27].

The essential oil gives *S. chamaecyparissus* flowers a specific aroma and flavor [8]. It is described somewhere between German and Roman chamomile, but less bitter than Roman chamomile and less sweet than German chamomile [28]. In contrast, the leaves have a strong camphoraceous odor and a bitter taste like tansy and wormwood [29]. However, from a taxonomic perspective, *S. chamaecyparissus* is recognized as a species complex, encompassing infraspecific taxa of uncertain systematic status but varying ploidy levels. These taxa, which include diploid, triploid, tetraploid, pentaploid, and hexaploid cytotypes, are morphologically indistinguishable, following the pattern of cryptic species [4,5,30]. Specifically, polymorphism, along with hybridization and multiple polyploidizations within the genus *Santolina*, leads to significant differences in the chemical profiles of species from this genus. This is a characteristic also observed in other genera within the Asteraceae family, such as the genus *Achillea* [31,32].

S. chamaecyparissus can be added to food, condiments, and beverages to enhance flavor and improve their properties, as well as to serve as a natural preservative [33,34]. Moreover, it can be incorporated into edible coatings for food packaging [35]. Additionally, it is valued for producing the natural yellow color typical of its flowers [36]. Furthermore, it has potential as an inhibitor of stainless-steel corrosion [37]. Moreover, it has potential for application in organic agriculture and for the development of biopesticides, due to its insecticidal [38–40], fungicidal [41], and herbicidal properties [42]. In addition to its wide range of biological activity, it is highly valuable as an ornamental plant [43], and as a plant suitable for green roofs [44].

The combination of two approaches—Gas Chromatography–Mass Spectrometry (GC–MS) as the primary chemical method for identifying essential oil composition, and the chemometrics technique, which applies statistical and mathematical methods to efficiently extract meaningful information from chemical data—was deemed effective for generating accurate and reliable results in authenticating *S. chamaecyparissus* essential oils [45]. Quantitative structure–retention relationship (QSRR) describes the relationship between a compound’s chemical structure and its predicted properties using molecular descriptors [46]. GC–MS provides precise, reproducible retention data, facilitating QSRR modeling [47]. The

relationship between molecular descriptors and experimentally obtained retention indices (RI_{exp}) can be modeled using machine learning algorithms [48] or artificial neural networks (ANNs). Aćimović et al. [49] revealed the reliability of the ANN models for predicting the RI s of compounds in *S. kitaibelii* essential oil determined by GC–MS. The results of Taheri-Garavand et al. [50] demonstrate the strong capability of ANN models to accurately predict the levels of 1,8-cineole, *p*-cymene, γ -terpinene, linalool, terpinene-4-ol, carvacrol, essential oil (EO), essential oil yield (EOY), and dry weight of *S. rechingeri*. Sabzi-Nojadeh et al. [51] compared the performance of the artificial neural network (ANN) and multilinear regression (MLR) to predict the essential oil yield and *trans*-anethole yield of fennel populations, demonstrating the potential of ANNs as a promising tool. This study employs ANN due to its proven effectiveness [46]. In summary, these chemometric tools combined with standard chemical analysis methods enhance the study of *S. chamaecyparissus* essential oil composition, particularly in identification, quantification, and authentication, as well as target potential biological biomarkers [42,52,53]. This integrated approach streamlines the analysis process and supports the standardization and quality assurance of essential oils for various applications, including aromatherapy, perfumery, pharmaceuticals, and food flavoring [54].

The aim of this research was to explore the chemical profile of *S. chamaecyparissus* flower essential oil from Serbia, determine its sensory profile through standard chemical analysis by GC–MS, and use the obtained results in chemometrics to construct a predictive model based on molecular descriptors. Additionally, the study aimed to conduct a literature-based analysis of the essential oils of this species, grouping them based on the dominant volatile compounds.

2. Materials and Methods

2.1. Plant Material

S. chamaecyparissus population from the IFVCNS (Institute of Field and Vegetable Crops Novi Sad, Serbia) collection was used in the study. This accession is confirmed and deposited at the BUNS Herbarium (University of Novi Sad, Serbia) under Voucher No. 2-1446 (Figure 1). Flowers were collected in June 2022 at full flowering stage, dried in the shade until reaching a constant weight (achieved after one week of drying) weight, and stored in multilayer paper bags until further analysis.

2.2. Essential Oil Isolation

S. chamaecyparissus essential oil was isolated by hydrodistillation using a Clevenger-type apparatus with approximately $90.0 \text{ g} \pm 5\%$ of the dried flower heads and 500 mL of water. Briefly, the mixture of plant material and water was placed in a flask connected to a glass apparatus consisting of a vertical tube combined with a condenser and a glass stopcock burette, and then heated. The process lasted for 2 h. This process was performed in triplicate. The essential oil yield (EOY) was calculated using the equation $EOY = (M/B_m) \times 100$, where M is the mass of the extracted oil (g) and B_m is the initial plant biomass (g).

2.3. Chemical Analysis

The *S. chamaecyparissus* essential oil was analyzed by gas chromatography with flame ionization detector (GC-FID) and gas chromatography coupled to mass spectrometry (GC–MS). The GC-FID and GC–MS analysis was performed using an Agilent 7890 gas-chromatograph coupled with Agilent 5975C mass selective detector and flame ionization detector on non-polar HP-5MS fused silica capillary column Agilent 19091S-433 (the conditions were replicated from Ref Adams [55] and thoroughly explained by Aćimović et al. [56]). The identification of constituents was carried out based on the linear reten-

tion index relative to C_8 – $C_{32}n$ -alkanes and compared with reference spectra (Wiley 7, NIST 17 and retention time locked Adams 4 databases) using Automated Mass spectral Deconvolution and Identification System (Amdis 32 ver 2.73) and NIST search ver. 2.3. The relative percentage of the oil constituents was expressed as percentages by FID peak area normalization.



Figure 1. *Santolina chamaecyparissus* (2-1446) deposited in BUNS herbarium.

2.4. Chemometric Analysis

2.4.1. Quantitative Structure–Retention Relationship (QSRR) Analysis

Molecular structure data, collected from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>, accessed on 12 December 2024), was provided as ASCII .smi files. Molecular descriptors for each compound were calculated using PaDel-Descriptor software [57] based on methods described by Dong et al. [58]. Given the large dataset, a genetic algorithm (GA) [51] implemented in Heuristic Lab (<https://dev.heuristiclab.com/trac.fcgi/>, accessed on 12 December 2024) was employed to select the most relevant descriptors for retention time prediction. GA was used to refine the predictive model for *S. chamaecyparissus* essential oil compounds, so-called quantitative structure–retention relationship (QSRR) analysis. Correlation analysis was also performed to identify and eliminate collinear descriptors.

2.4.2. Artificial Neural Network (ANN)

A multi-layer perceptron (MLP) model, consisting of input, hidden, and output layers, was used due to its ability to approximate nonlinear functions [59]. The Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm was applied for ANN training, with input and output data normalized to enhance model performance. The dataset was randomly split into training (60%), testing (20%), and validation (20%) subsets. ANN results, including weight values, depended on initial parameter assumptions [60]. Various network topologies with 1 to 20 hidden neurons were tested, running 100,000 iterations with random weight and bias initialization. Model optimization was based on minimizing validation error, and statistical analysis was conducted using Statistica 10 (Statistica, 2010).

2.4.3. Global Sensitivity Analysis

Yoon’s interpretation method [61] was used to assess the relative influence of molecular descriptors on retention time based on the weight coefficients of the trained ANN.

2.5. Sensory Analysis

The sensory evaluation aimed to assess the odor of *S. chamaecyparissus* essential oil, following the methodology described by Tsitlakidou et al. [62]. A panel of fifteen experts conducted the evaluation in a specialized laboratory. The descriptive analysis covered fifteen aroma attributes, including herbal, woody, spicy, terpenic, minty, fruity, camphoraceous, balsamic, green, and earthy. Each essential oil sample was evaluated in triplicate using a 10-point interval scale (0 = none, 9 = extra strong). For odor detection, one centimeter of a smelling strip was dipped into each sample, and panelists took three quick, deep sniffs before removing the strip. Evaluations were performed with 20 s intervals between samples, ensuring clean air breaks between assessments.

2.6. Statistical Analysis

The cluster analysis was conducted to determine the similarity between observed samples. The collected data were processed statistically using the software package STATISTICA 10.0, while the heat map was performed by the R software 4.0.3 (64-bit version) to visually investigate the likenesses among various compounds.

3. Results

3.1. Chemical Composition of *S. chamaecyparissus* Essential Oil

The yield of essential oil from the dried flower heads of *S. chamaecyparissus* was 0.48 mass %. The oil was a yellow oily liquid, with an aroma similar to that of the plant material.

In the *S. chamaecyparissus* flower essential oil, 47 compounds were identified (Table 1, Figure 2). The dominant class was oxygenated monoterpenes, comprising 44.71%, with artemisia ketone (36.11%) as the main compound. Oxygenated sesquiterpenes make up 30.15%, with vulgarone B (22.13%) as the dominant compound.

Table 1. Chemical profile of *Santolina chamaecyparissus* flower essential oil.

Peak	Compound	Class	R.t.	RI _{exp}	RI _{lit}	%	Odor Type [#]
1	α -Pinene	MT	5.972	927	932	0.19	herbal
2	Camphene	MT	6.373	944	946	0.71	woody
3	Sabinene	MT	7.058	965	969	0.43	woody
4	β -Pinene	MT	7.167	970	974	1.41	herbal
5	Myrcene	MT	7.557	987	988	0.68	spicy

Table 1. Cont.

Peak	Compound	Class	R.t.	RI _{exp}	RI _{lit}	%	Odor Type #
6	Yomogi alcohol	OMT	7.772	997	999	1.30	-
7	α -Terpinene	MT	8.440	1015	1014	0.09	woody
8	<i>p</i> -Cymene	MT	8.698	1021	1020	0.18	terpenic
9	β -Phellandrene	MT	8.851	1025	1025	0.92	minty
10	1,8-Cineole	OMT	8.910	1027	1026	0.77	herbal
11	Artemisia ketone	OMT	10.032	1054	1056	36.11	herbal
12	Artemisia alcohol	OMT	10.833	1075	1080	0.72	herbal
13	2-Methyl butyl isovalerate	O	11.668	1095	1103	0.11	fruity
14	<i>cis-p</i> -Menth-2-en-1-ol	OMT	12.525	1116	1118	0.17	-
15	<i>trans</i> -Pinocarveol	OMT	13.105	1131	1135	0.22	herbal
16	Camphor	OMT	13.310	1136	1141	2.23	camphoreous
17	Chrysanthemyl alcohol	OMT	14.001	1153	1158	0.19	-
18	Pinocarvone	OMT	14.102	1156	1160	0.08	minty
19	Borneol	OMT	14.227	1159	1165	1.12	balsamic
20	Terpinen-4-ol	OMT	14.748	1171	1174	0.63	spicy
21	Cryptone	NOMT	15.100	1180	1183	1.03	-
22	α -Terpineol	OMT	15.328	1186	1186	0.07	terpenic
23	Myrtenal	OMT	15.560	1192	1195	0.33	herbal
24	3Z-Hexenyl 2-methyl butanoate	O	17.183	1229	1229	0.12	green
25	<i>p</i> -Menth-1en-7-al	OMT	19.048	1271	1273	0.29	-
26	Carvacrol	OMT	20.254	1299	1298	0.48	spicy
27	α -Longipinene	ST	22.425	1348	1350	0.91	-
28	<i>trans</i> -Caryophyllene	ST	25.445	1417	1417	0.22	spicy
29	<i>allo</i> -Aromadendrene	ST	27.213	1460	1458	0.63	woody
30	<i>ar</i> -Curcumene	ST	28.14	1482	1479	2.86	-
31	1-Pentadecene	O	28.529	1491	1493	0.28	-
32	δ -Cadinene	ST	29.843	1522	1522	0.29	herbal
33	Italicene ether	OST	30.275	1533	1536	0.32	-
34	Spathulenol	OST	32.038	1575	1577	3.41	earthy
35	Caryophyllene oxide	OST	32.248	1580	1582	0.99	woody
36	Salvial-4(14)-en-1-one	OST	32.684	1590	1594	0.37	-
37	NI-1	NI *	32.886	1595	/	3.26	-
38	NI-2	NI *	33.207	1603	/	1.03	-
39	β -Oplophenone	OST	33.273	1605	1607	0.72	-
40	6-methyl-6-(3-methylphenyl)-Heptan-2-one	O	34.373	1635	1639	0.36	-
41	Vulgarone B	OST	34.928	1649	1649	22.13	-
42	(Z,Z)-1,8,11-Heptadecatriene	O	35.211	1658	1659	0.18	-
43	NI-3	NI *	35.368	1661	/	0.97	-
44	Khusinol	OST	35.954	1678	1675	0.20	-
45	Germacra-4(15),5,10(14)-trien-1- α -ol	OST	36.248	1685	1685	0.78	-
46	Amorpha-4,9-dien-2-ol	OST	36.899	1703	1700	0.93	-
47	Cyclocolorenone	OST	38.928	1758	1759	0.30	-
Monoterpene hydrocarbons		(MT)				4.61	
Oxygenated monoterpenes		(OMT)				44.71	
Noroxxygenated monoterpenes		(NOMT)				1.03	
Sesquiterpene hydrocarbons		(ST)				4.91	
Oxygenated sesquiterpenes		(OST)				30.15	
Other		(O)				1.05	
Not identified		(NI *)				5.26	

Rt—retention time; RI_{exp}—retention indices experimentally obtained at non-polar HP-5MS fused silica capillary relative to C₈–C₃₂*n*-alkanes; RI_{lit}—retention indices according to reference spectra (Wiley 7, NIST 17, Adams 4 databases); # Odor type according to the Good Scents Company Information System (<http://www.thegoodscentscompany.com/> accessed on 20 January 2025.) * Ten most abundant ions of NI compounds, *m/z* (relative intensity): NI-1: 119(99), 105(44), 106(42), 91(40), 120(29), 107(28), 121(28), 108(22), 147(181), 41(165) NI-2: 93(99), 135(80), 107(69), 91(57), 79(53), 175(53), 41(50), 134(48), 108(44), 55(42) NI-3: 93(99), 81(80), 136(59), 79(57), 95(53), 41(53), 107(49), 91(48), 159(47), 121(42).

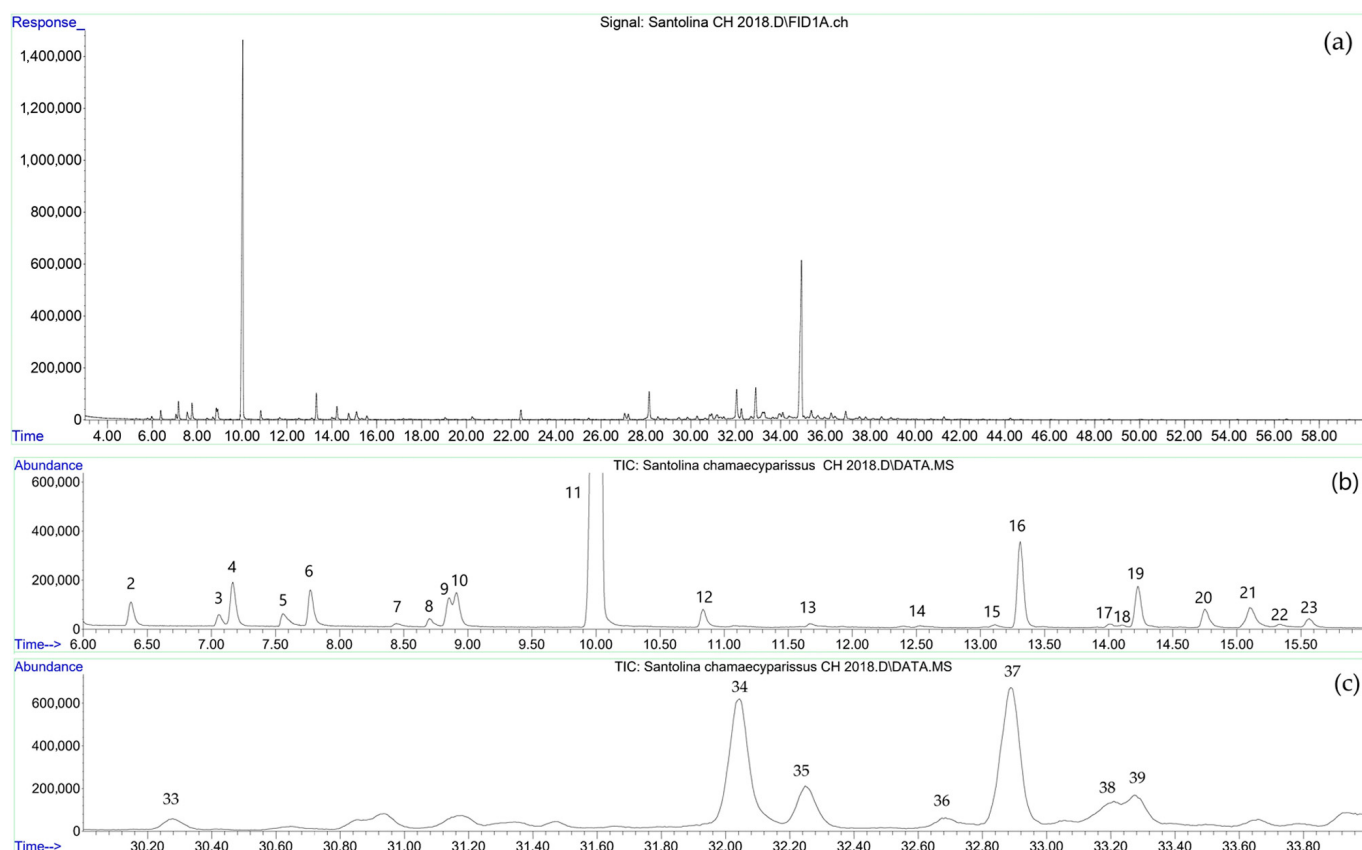


Figure 2. GC–MS chromatogram of *Santolina chamaecyparissus* flower essential oil: (a) full chromatogram; (b) enlarged view of the 6–16 min zone; (c) enlarged view of the 30–34 min zone.

3.2. Chemometric Analysis of *S. chamaecyparissus* Essential Oil

In QSRR analysis, molecular descriptors numerically encode the structural properties of compounds analyzed by GC–MS. PaDel-Descriptor software was used to calculate these descriptors, which are essential for QSRR modeling. Before applying a genetic algorithm (GA), factor analysis was conducted to remove highly correlated descriptors, retaining only one from each correlated group. GA was then employed to select the most relevant descriptors using an evolutionary simulation approach.

The initial GA population was randomly generated, with the number of so-called genes equal to the molecular descriptors obtained from PaDel-Descriptor. The probability of generating zero for a gene was set at a minimum of 60% to maintain a small subset. The simulation used crossover (90% probability) and mutation (0.5%) operators. A population size of 100 so-called genes evolved over 50 generations, with the process terminating when 90% of generations had the same fitness value. As a result, eight key molecular descriptors were selected, and the correlation matrix among these descriptors is presented in Table 2.

The calibration and predictive performance of the QSRR model were evaluated through validation, with the squared correlation coefficient (R^2) used as an indicator of model fitness. To capture the nonlinear relationship between retention indices (RIs) and selected molecular descriptors, an artificial neural network (ANN) model was developed. The statistical results of the MLP 12-4-1 network are presented in Table 3, while Figure 3 presents the predicted RIs, demonstrating the ANN model's predictive accuracy by illustrating the correlation between predicted and experimental retention values.

Table 2. The correlation coefficient matrix for the selected molecular descriptors by GA.

	¹ AATSC7m	¹ AATSC1e	¹ AATSC3e	² SM1_DzZ	² VR2_Dzm	³ ETA_Beta_ns	⁴ Mc-Gowan_Volume	⁵ MDEC-11
¹ AATSC7m		0.014 <i>p</i> = 0.969	−0.145 <i>p</i> = 0.689	−0.103 <i>p</i> = 0.778	−0.156 <i>p</i> = 0.667	−0.443 <i>p</i> = 0.199	0.016 <i>p</i> = 0.965	0.364 <i>p</i> = 0.301
¹ AATSC1e			0.134 <i>p</i> = 0.712	−0.446 <i>p</i> = 0.197	−0.111 <i>p</i> = 0.761	−0.226 <i>p</i> = 0.531	0.140 <i>p</i> = 0.699	−0.276 <i>p</i> = 0.441
¹ AATSC3e				−0.485 <i>p</i> = 0.155	0.248 <i>p</i> = 0.489	0.167 <i>p</i> = 0.644	0.015 <i>p</i> = 0.968	−0.411 <i>p</i> = 0.238
² SM1_DzZ					−0.164 <i>p</i> = 0.650	−0.021 <i>p</i> = 0.955	−0.107 <i>p</i> = 0.769	−0.057 <i>p</i> = 0.876
² VR2_Dzm						−0.297 <i>p</i> = 0.404	0.283 <i>p</i> = 0.428	−0.027 <i>p</i> = 0.941
³ ETA_Beta_ns							0.008 <i>p</i> = 0.984	−0.298 <i>p</i> = 0.403
⁴ Mc-Gowan_Volume								−0.224 <i>p</i> = 0.534

¹ 2D Autocorrelation molecular descriptors: AATSC7m—Average centered Broto–Moreau autocorrelation, lag 7/weighted by mass; AATSC1e—Average centered Broto–Moreau autocorrelation, lag 1/weighted by Sanderson electronegativities; AATSC3e—Average centered Broto–Moreau autocorrelation, lag 3/weighted by Sanderson electronegativities; ² 2D Barysz matrix molecular descriptors: SM1_DzZ—Spectral moment of order 1 from Barysz matrix/weighted by atomic number; VR2_Dzm—Normalized Randic-like eigenvector-based index from Barysz matrix/weighted by mass; ³ 2D Extended topochemical atom molecular descriptor: ETA_Beta_ns—a measure of electron-richness of the molecule; ⁴ 2D McGowan volume molecular descriptor: McGowan_Volume—McGowan characteristic volume; ⁵ 2D Molecular distance edge molecular descriptor: MDEC-11—Molecular distance edge between all primary carbons.

Table 3. Summary of ANN model performance and error metrics across training, testing, and validation phases.

Net. Name	Performance			Error			Training Algorithm	Error Function	Activation	
	Train.	Test.	Valid.	Train.	Test.	Valid.			Hidden	Output
MLP 8-8-1	0.980	0.979	0.998	1588.284	870.025	658.181	BFGS 59	SOS	Exp.	Exp.

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.

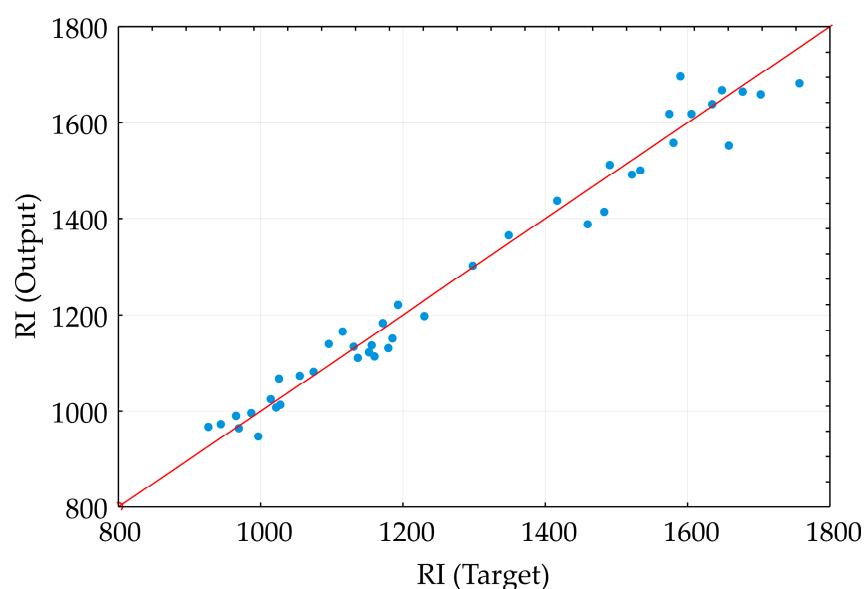


Figure 3. Comparison of experimentally obtained RIs with ANN-predicted values.

The training cycle yielded the highest prediction accuracy for RIs, as it utilized a larger dataset compared to the testing and validation phases. This is evident from Table 3, where the training set achieved an R^2 of 0.998, while the testing and validation sets showed lower

values. Higher accuracy in the training phase is expected, as these data were used for ANN modeling, whereas the testing and validation sets assessed the model's generalization. The results confirm the reliability of the ANN model for predicting the retention indices of *S. chamaecyparissus* essential oil compounds analyzed by GC–MS.

Molecular descriptors are numerical values that encode the structural and physicochemical properties of the molecules, aiding in QSRR modeling, see Figure 4. These descriptors collectively enable the identification of key molecular features affecting retention time, quantification of steric, electronic, and topological influences on chromatographic behavior, and improved artificial neural network (ANN)-based predictions by selecting relevant descriptors for QSRR modeling.

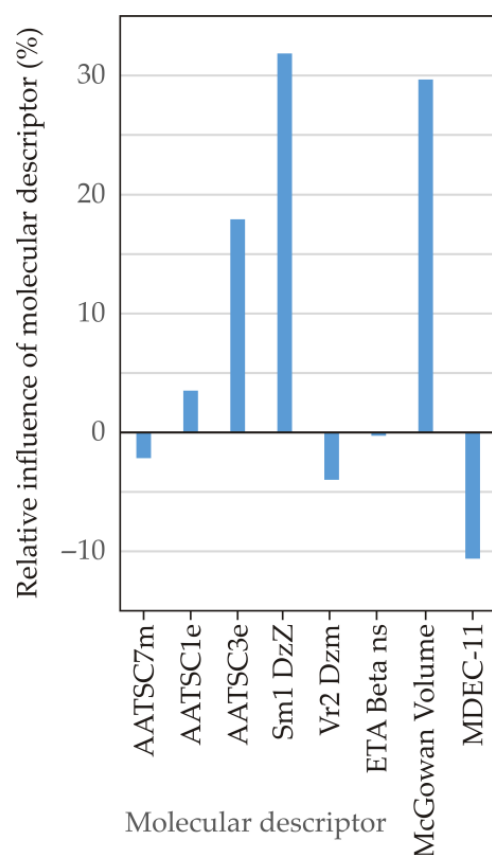


Figure 4. The relative importance of the molecular descriptors on RI, determined using Yoon interpretation method.

The global sensitivity analysis results highlight the relative influence of molecular descriptors on retention indices (RI), revealing key structural and physicochemical factors affecting retention behavior in gas chromatography. SM1_DzZ (+31.86%) and McGowan_Volume (+29.66%) exhibit the highest positive influence, indicating that atomic connectivity and molecular size significantly contribute to retention, as larger molecules with higher atomic connectivity tend to interact more strongly with the stationary phase. AATSC3e (+17.92%) also positively affects RI, suggesting that medium-range electronegativity correlations impact retention by influencing molecular polarity and interactions. AATSC1e (+3.53%) has a moderate positive effect, reinforcing the role of electronegativity-based interactions but at a shorter atomic distance. In contrast, VR2_Dzm (−3.98%) and MDEC-11 (−10.61%) negatively influence RI, implying that molecular branching and mass-weighted connectivity contribute to shorter retention times, possibly due to steric effects or weaker interactions with the stationary phase.

3.3. Sensory Analysis of *S. chamaecyparissus* Essential Oil

The average of the odor description intensities was plotted on a spider diagram in Figure 5. In the *S. chamaecyparissus* essential oil, all evaluators identified a herbal odor as the dominant odor with the highest intensity (8–9), followed by moderate contributions from earthy, woody, and camphoreous, while fruity, minty, and terpenic characteristics are minimal, scoring closer to 1–2.

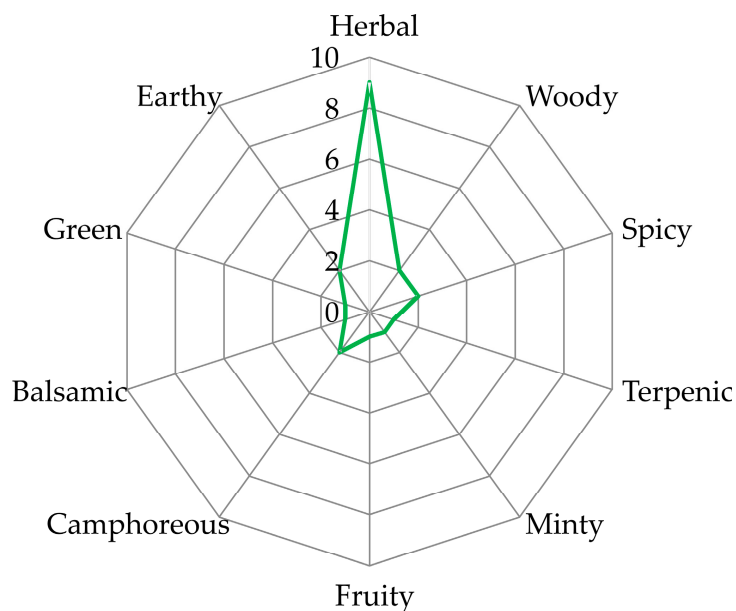


Figure 5. Results of the sensory analysis of the *Santolina chamaecyparissus* essential oil.

4. Discussion

The essential oil is pale yellow to dark yellow or greenish-yellow in color, and its content ranges from 0.06 to 2.10%, depending on the origin, variety, plant part, and method of extraction (Table 4).

Table 4. Essential oil content in *Santolina chamaecyparissus* from Serbia (TS) and a literature-based analysis (references are listed from newest to oldest).

Reference	Origin	Plant Part	Method of Extraction	Essential Oil Content (%)
TS	Serbia	Flowers	HD	0.48
[63]	Saudi Arabia	Aerial parts	HD	0.76
[34]	Turkey	Leaves	HD	0.75
[64]	Turkey	Aerial parts	MAE	0.60
[10]	Algeria	Aerial parts	HD	0.85
[65]	Greece	Aerial parts	HD	0.33
[39]	Poland	Aerial parts	HD	1.11
[26]	Tunisia	Flowers Root	HD	0.06 0.15
[25]	Syria	Leaves	HD	2.10
[66]	Algeria	Aerial parts	SD	0.80
[67]	Spain	Aerial parts	HD	1.00
[68]	Spain	Flowers	HD SFE	0.10–0.50 0.10–1.40

Table 4. *Cont.*

Reference	Origin	Plant Part	Method of Extraction	Essential Oil Content (%)
[69]	India	Aerial parts	HD	0.10–1.10
[70]	India	Aerial parts	HD	1.10
[71]	Turkey	Aerial parts	HD	1.60
[72]	Spain	Aerial parts	SD	0.18–1.55
[73]	Spain	Aerial parts	HD	0.40
[29]	India	N/A	HD	0.40–0.50

TS—this study; HD—hydrodistillation; MAE—microwave assisted distillation; SD—steam distillation; SFE—supercritical fluid extraction; N/A—not applicable.

Although a significant number of studies have investigated the essential oil content of *S. chamaecyparissus*, only two previous publications specifically focus on the flowers. According to these studies, flowers from Tunisia contain 0.06% essential oil [26], while samples from Spain contain between 0.1% and 0.5%, depending on the mean particle size separated by a series of sieves (0.4, 0.6, and 0.8 mm) [68]. In both of these studies, the hydrodistillation method was used to obtain essential oil, as was the case in the present study. In the Spanish study, dried flowers were used, and the yield aligns with our results. In contrast, the Tunisian study calculated the essential oil yield based on the fresh weight of the plant, which explains the significantly lower value.

The chemical profile of the *S. chamaecyparissus* essential oil is influenced by sub-species [64], climatic and environmental conditions [60], cultivation technique [43], time of harvest [14], development stage [66], as well as the method of extraction [59]. A review of the literature revealed 19 scientific papers that focus on the study of the *S. chamaecyparissus* essential oil (Table 5).

Table 5. Essential oil content in *Santolina chamaecyparissus* from Serbia (TS) and a literature-based analysis (references are listed from newest to oldest).

Sample No	Artemisia Ketone	Camphor	1,8-Cineole	Myrcene	Borneol	β-Phellandrene	p-Cymene	Cubanol	Terpinen-4-ol	trans-p-Mentha-2,8-dienol	Sum of Marker Compounds	Plant Part; Method of Extraction	Origin	Reference
1	36.1	2.2	0.8	0.7	1.1	0.9	0.2	0.0	0.6	0.0	42.6	F; HD	Serbia	TS
2	0.0	0.5	0.0	0.0	2.1	0.4	0.0	0.0	1.4	54.0	58.4	AP; HD	Saudi Arabia	[63]
3	39.8	17.7	0.0	2.9	1.2	8.0	0.0	0.0	0.0	0.0	69.6	AP; MAE	Turkey	[65]
4	6.8	0.0	0.0	27.4	0.0	17.2	0.0	0.0	0.0	0.0	51.4	FS; N	China	[43]
5	9.9	0.0	0.0	24.1	0.0	18.1	0.0	0.0	0.1	0.0	52.2	*		
6	42.0	2.5	0.0	7.7	1.0	8.3	0.2	3.4	0.1	0.0	65.2	AP; HD	Algeria	[10]
7	2.6	0.0	9.8	0.0	1.4	0.0	1.4	0.0	2.1	0.0	17.3	AP; SD	Spain	[38]
8	25.9	2.8	0.5	9.2	1.0	18.7	0.2	0.0	0.6	0.0	58.9	AP; HD	Poland	[39]
9	0.1	5.3	12.9	3.0	3.7	0.0	0.8	0.0	7.0	0.0	32.8	F; HD	Tunisia	[26]
10	15.7	2.4	0.6	7.4	1.3	10.6	0.0	0.0	0.9	0.0	38.9	L; HD	Syria	[25]
11	0.0	0.0	11.2	6.4	0.3	0.0	1.5	0.0	6.1	0.0	25.5	AP; SD	Algeria	[66]

Table 5. Cont.

Sample No	Artemisia Ketone	Camphor	1,8-Cineole	Myrcene	Borneol	β -Phellandrene	p-Cymene	Cubenol	Terpinen-4-ol	trans-p-Mentha-2,8-dienol	Sum of Marker Compounds	Plant Part; Method of Extraction	Origin	Reference
12	0.0	1.8	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.3	AP; HD	Saudi Arabia	[14]
13	0.0	0.7	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.1	**		
14	27.2	3.9	0.0	6.9	0.0	7.5	0.0	0.0	0.0	0.0	45.5	AP; HD	Spain	[67]
15	15.7	2.5	17.8	0.6	14.3	1.5	0.0	0.0	1.3	0.0	53.8	AP; HD	Egypt	[74]
16	16.6	2.1	19.6	0.4	7.4	1.2	0.0	0.0	1.8	0.0	49.1	***		
17	0.0	0.8	0.3	0.4	1.1	0.3	32.8	0.0	0.8	0.0	36.5	F; HD	Spain	[68]
18	0.0	2.2	1.8	0.3	0.2	3.8	0.3	0.0	0.1	0.0	8.7	F; SFE		
19	0.0	0.0	0.5	7.0	1.6	0.0	0.3	0.0	2.6	0.0	12.0	AP; HD	India	[69]
20	0.0	0.0	13.5	0.0	1.6	0.0	0.0	0.0	1.7	0.0	16.8	****		
21	31.8	1.9	15.6	14.2	0.0	0.0	0.2	0.0	2.9	0.0	66.6	AP; HD	India	[70]
22	38.1	11.7	0.0	4.3	0.9	9.2	0.3	0.0	1.1	0.0	65.6	AP; HD	Turkey	[71]
23	0.1	9.2	8.7	0.1	11.6	0.0	1.3	1.6	3.4	0.0	36.0	AP; SD ****	Spain	[73]
24	4.5	24.9	7.2	0.2	12.8	0.0	1.4	1.7	3.5	0.0	56.2			
25	2.8	18.9	2.3	tr	26.0	0.0	0.8	1.6	3.1	0.0	55.5			
26	1.5	tr	6.0	0.3	11.3	0.0	1.6	6.7	4.4	0.0	31.8			
27	1.2	22.5	17.6	0.1	28.4	0.0	1.1	0.4	5.1	0.0	76.4			
28	0.1	42.9	0.3	0.1	8.4	0.0	0.2	17.3	1.0	0.0	70.3			
29	0.1	8.3	2.9	0.2	2.3	0.0	0.9	12.9	2.4	0.0	30.0			
30	27.8	2.0	2.8	0.9	0.9	0.0	0.4	1.7	1.1	0.0	37.6			
31	25.6	4.7	13.2	16.1	0.6	0.0	0.1	8.6	0.8	0.0	69.7			
32	45.0	1.5	2.0	15.0	1.5	5.0	0.5	0.0	0.4	0.0	70.9	L; HD	France	[75]
33	0.0	0.0	0.0	0.0	0.0	0.0	33.0	0.0	0.0	0.0	33.0	N/A; HD	India	[29]

TS—this study; HD—hydro distillation; MAE—microwave assisted distillation; SD—steam distillation; SFE—supercritical fluid extraction; N/A—not applicable; F—flowers; AP—aerial parts; FS—foliage sprouts; N—extraction with liquid nitrogen; L—leaves; *—micropropagated and naturally grown; **—time of harvest (spring and summer); ***—stage of development (bud and flowering); ****—climate zone (subtropical and temperate); *****—ssp from wild and cultivated populations; tr—trace.

By reviewing the studies listed in Table 5, it is evident that only two have analyzed the essential oil from *S. chamaecyparissus* flowers [26,68]. These two studies report quite different essential oil profiles. For example, in the Tunisian sample, oxygenated monoterpenes dominate (36.9%), followed by oxygenated sesquiterpenes (29.8%) and sesquiterpene hydrocarbons (16.8%) [26]. The major individual components include 1,8-cineole (12.9%), β -eudesmol (10.5%), terpinene-4-ol (6.97%), γ -cadinene (6.55%), spathulenol (5.80%), camphor (5.27%), and germacrene D (5.03%). On the other hand, the Spanish sample is dominated by oxygenated monoterpenes (56.3–64.4%), primarily thymol (35.4–41.6%), followed by p-cymene (28.9–34.8%), with the proportions varying according to particle size [68]. In the present study, the dominant component is artemisia ketone (36.1%). This diversity in essential oil profiles is primarily attributed to differences among subspecies [73,76]. Considering that the species *S. chamaecyparissus* is highly complex and includes a large number of subspecies (among them *squarrosa*, *incana*, *pecten*, *magonica*, *insularis*, *ericoides*, *tomentosa*, and *viridis*), these variations appear completely logical. Our study highlights the need for a detailed investigation that would link the morphological and chemical characteristics of this species to identify potential chemotaxonomic markers. (*squarrosa*, *incana*, *pecten*, *magonica*, *insularis*, *ericoides*, *tomentosa*, *viridis*).

The hierarchical clustering dendrogram, see Figure 6, constructed using complete linkage and Manhattan distances, reveals distinct groupings of *S. chamaecyparissus* samples based on their volatile compound composition. The clustering reflects chemical similarities among the samples, which can be traced back to key compounds in the table. One major cluster includes samples with high artemisia ketone content, such as this study from Serbia (36.1%) and Spain (27.8%) [73], suggesting a chemically distinct subgroup dominated by this compound. Another grouping appears to cluster samples rich in β -phellandrene, such as naturally grown samples from China (18.1%) [43] and Poland (18.7%) [39], indicating a common biochemical profile. Similarly, camphor-rich samples, including Turkey (17.7%) [64], tend to cluster together, likely due to their shared oxygenated monoterpene profile. Additionally, a separate grouping is evident for samples with high 1,8-cineole concentrations, such as samples from Egypt collected at the bud stage (17.8%) and the flowering stage (19.6%) [74], linking them to cineole-dominant chemotypes. The presence of trans-*p*-mentha-2,8-dienol exclusively in Saudi Arabia (54.0%) [63] suggests it is an outlier, potentially forming its own distinct cluster. The overall clustering pattern highlights how specific chemical markers define the differentiation among *S. chamaecyparissus* samples, correlating with their geographical origin, extraction methods, and genetic variations.

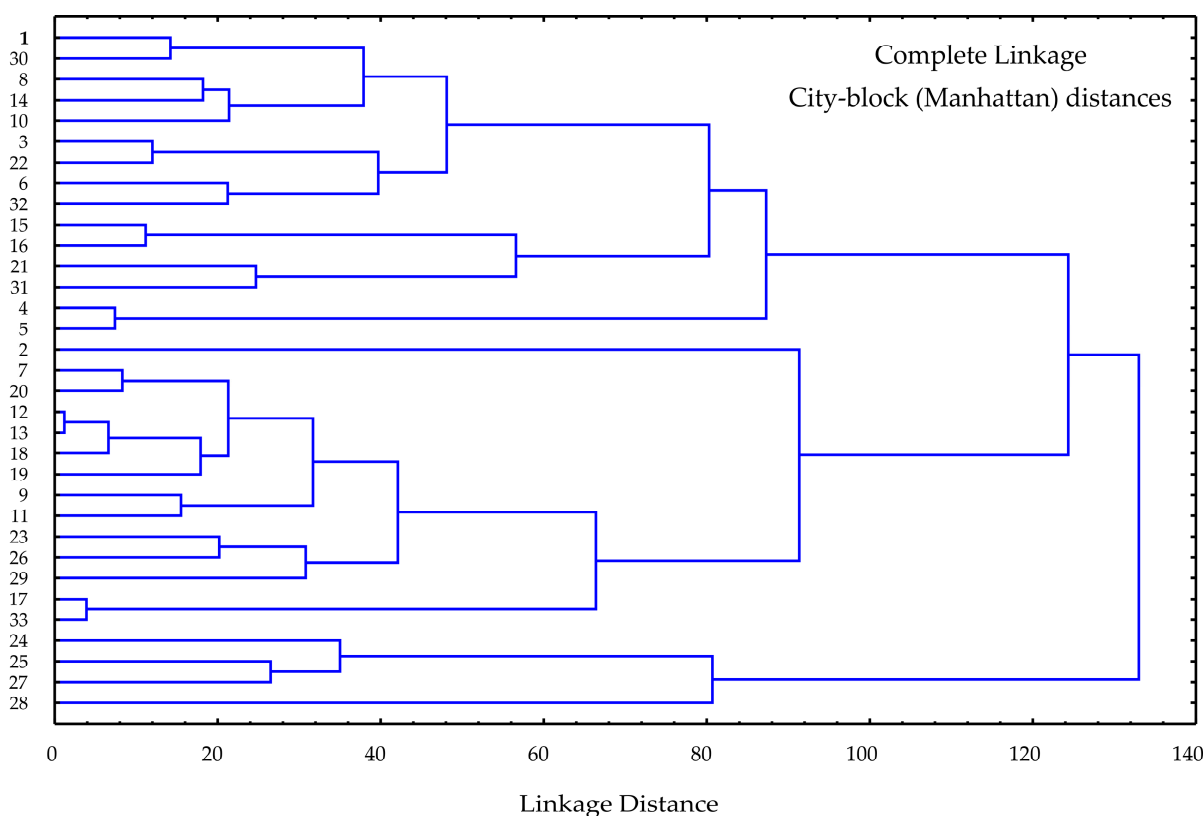


Figure 6. Cluster analysis of the observed samples.

The color correlation analysis, see Figure 7, illustrates how different compounds in *S. chamaecyparissus* essential oil are related to each other. Darker colors indicate a stronger correlation, meaning those compounds frequently appear together in significant amounts. Lighter colors suggest weaker correlations, implying these compounds do not have a strong relationship. The results of correlation analysis revealed strong positive relationships between borneol and camphor, Artemisia ketone and 1,8-cineole, as well as *p*-cymene and β -phellandrene, suggesting similar biosynthetic pathways or co-extraction tendencies. On the other hand, β -phellandrene and camphor, along with trans-*p*-mentha-2,8-dienol and

borneol, exhibit strong negative correlations. Cubenol shows mixed correlations, implying an inconsistent relationship with other compounds.

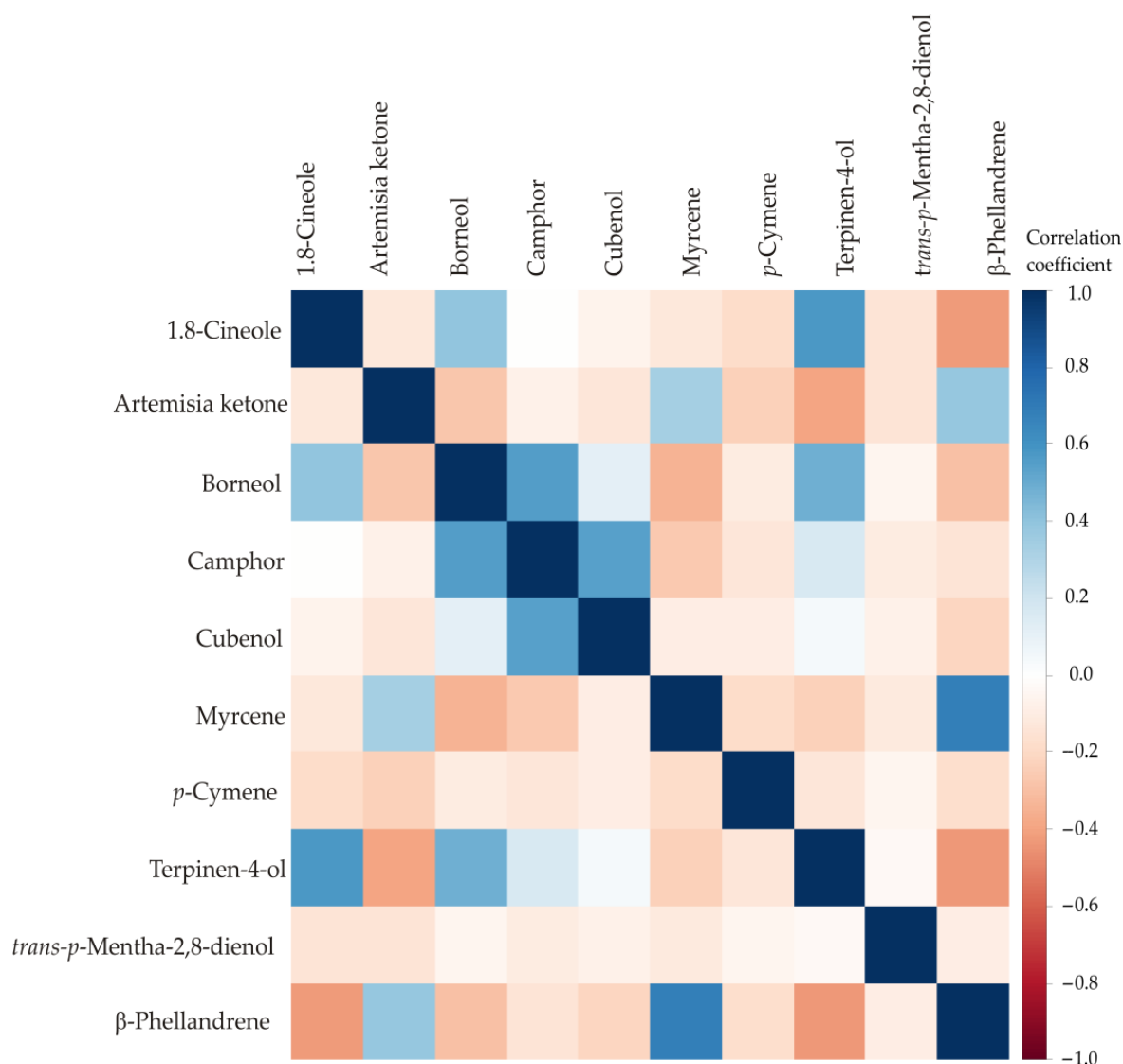


Figure 7. Color correlation graph the 10 most significant GC/MS identified compounds indifferent *Santolina chamaecyparissus* essential oil samples according to Table 5.

The correlation analysis among the major compounds in the dataset reveals several statistically significant relationships ($p < 0.05$), highlighting potential biosynthetic or functional linkages between specific constituents. Notably, terpinen-4-ol shows a strong positive correlation with 1,8-cineole ($r = 0.5699$, $p = 0.001$) and borneol ($r = 0.4831$, $p = 0.004$), suggesting these compounds may share similar metabolic pathways. Myrcene is significantly correlated with β -phellandrene ($r = 0.6822$, $p < 0.001$), while camphor exhibits a strong positive correlation with borneol ($r = 0.5511$, $p = 0.001$) and cubenol ($r = 0.5478$, $p = 0.001$), indicating possible co-accumulation. The sum of marker compounds correlates significantly with artemisia ketone ($r = 0.5704$, $p = 0.001$) and camphor ($r = 0.4710$, $p = 0.006$), reflecting their substantial contribution to the overall profile. In contrast, *trans-p*-mentha-2,8-dienol and *p*-cymene show minimal and non-significant correlations with most other compounds, implying more independent variation. These patterns suggest specific clusters of compounds may be co-regulated or share biosynthetic origins in *Artemisia* spp. under the studied conditions.

By combining GC–MS analytical data and sensory profiles, chemometrics can act as a tool for quality screening of *S. chamaecyparissus* essential oil [77–79]. QSRR establishes a predictive model for compound RI, ANN improves prediction accuracy, molecular descriptors provide essential input data, and GA optimizes descriptor selection [80]. This integrated approach allows for efficient, accurate, and automated profiling of essential oils, reducing experimental workload while improving reliability [81].

5. Conclusions

The essential oil of *Santolina chamaecyparissus* from Serbia comprises 47 identified compounds, making up 91.72% of the total oil. Oxygenated monoterpenes (44.71%), particularly artemisia ketone (36.11%), and oxygenated sesquiterpenes (30.15%), dominated by vulgarone B, are the primary constituents. A QSRR model was developed to predict the retention times of these compounds, demonstrating high accuracy. Using eight molecular descriptors selected via a genetic algorithm, the ANN model achieved a coefficient of determination (R^2) of 0.980, indicating strong predictive reliability. Sensory analysis revealed a dominant herbal aroma with earthy, woody, and camphor notes. Significant variability in essential oil composition across studies was observed, influenced by geographic origin, environmental conditions, and extraction methods. Cluster analysis identified distinct chemical profiles based on key compounds like artemisia ketone, β -phellandrene, camphor, and 1,8-cineole. These findings deepen the understanding of *S. chamaecyparissus* essential oil's chemical diversity and potential applications in medicine, food science, and agriculture. Future research should explore the bioactivity of specific chemotypes and the influence of environmental and genetic factors on composition. The developed QSRR model provides a valuable tool for further exploration of essential oil properties and applications.

Author Contributions: Conceptualization, B.L., M.R. and M.A.; methodology, M.C. and J.S.J.; software, L.P.; validation, M.C., J.S.J. and J.F.; formal analysis, M.C. and J.S.J.; investigation, B.L. and M.R.; resources, M.A.; data curation, L.P.; writing—original draft preparation, B.L.; writing—review and editing, M.R.; visualization, J.F.; supervision, J.S.J.; project administration, M.A.; funding acquisition, B.L., M.C., M.R., J.F. and M.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant Numbers: 451-03-136/2025-03/200134 (B.L.), 451-03-66/2024-03/200026 (M.C.; J.S.J.), 451-03-136/2025-03/200125 and 451-03-137/2025-03/200125 (M.R.), 451-03-136/2025-03/200222 (J.F.), 451-03-136/2025-03/200051 (L.P.), 451-03-136/2025-03/200032 (M.A.).

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ANN	Artificial Neural Network
BUNS	Botanical Collections at the University of Novi Sad
GA	Genetic Algorithm
GC–MS	Gas Chromatography–Mass Spectrometry
IFVCNS	Institute of Field and Vegetable Crops Novi Sad
MLP	Multi-Layer Perceptron
QSRR	quantitative structure–retention relationship

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