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Metabolic Correlations of *Salvia dugesii* Fernald and *Salvia gesneriiflora* Lindl. & Paxton with Native *Salvia* Plants from Four Continents Using Essential Oils Compositions

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Abstract: Several applications of natural products around the world arise from traditional knowledge or evident organoleptic properties, and essential oils from *Salvia* species are a current example. The genus is integrated by native and endemic species from Africa, the Americas, Asia, and Europe. In the present work, essential oil compositions of *Salvia dugesii* and *S. gesneriiflora* were experimentally determined and statistically correlated with ten described *Salvia* species from four continents by using multivariate methods complemented with univariate analysis and PCA protocols, to establish metabolic approaches. Essential oils data from *S. angulata*, *S. miltiorrhiza*, *S. plebeia*, *S. sclarea*, *S. argentea*, *S. viridis*, *S. lavandulifolia*, *S. africana-lutea*, *S. chamelaeagnea*, and *S. officinalis* were included in the study. By the above, 146 essential oil components, classified into 29 structural skeletons, according to its biogenesis, were analyzed. The results provided metabolic similarities between American and Asian *Salvia* species due to a higher active sesquiterpene metabolism; and African and European species revealed chemical similarities, since monoterpene pathways dominate. Such correlations are in concordance with genetic knowledge about genus, thereby, approaches on metabolism of *Salvia* can be easily visualized using statistical tools, consequently, practical method to analyze Salvias for scientific proposes.

Keywords: *Salvia*; *Salvia dugesii*; *Salvia gesneriiflora*; Lamiaceae; essential oil metabolism; chemometric analysis.

1. Introduction

The genus *Salvia* is one of the most important genera of the Lamiaceae family, with nearly 1000 species growing on five continents, despite Australia/Oceania is the unique continent without native species [1]. Phytochemical investigations showed that *Salvia* species metabolize, phenolics

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[2,3] and terpenoids as the main components [4], highlighting essential oils, which confer numerous applications, where caryophyllene (**8**) probably is considered the representative structural skeleton of the genus [5,6], however, some differences in the composition of the essential oils from a plant are determined by the individuality of species, environmental aspects, agronomic conditions, plant harvest time, and processing time of the raw material, as expectable [7-9]. The essential oils from several *Salvia* species are valuable sources for screening applications in the pharmaceutical industry, including antimicrobial, antioxidant, and cytotoxic activities [10-12], as well as supplies used in the cosmetic and food industries [5, 13].

Apparently, the study and use of the above applications could be limited for those endemic species, however, a systematic study to expose the metabolic similarity to well-known medicinal or commercial plants could remove such limitation. Thus, the possibility to correlate plants from the genus, but different world locations to propose metabolism similarities and rational applications, according to chemical compositions becomes pertinent. These approaches can be achieved by statistical methods, and *Salvia* seems to be a suitable genus to reveal the above-mentioned due to its well-known applications, and current chemotype correlation attempts [14-16].

In the present work, essential oils compositions of *S. dugesii*, and *S. gesneriiflora* are described for the first time, and metabolic correlations of experimental data with described data from *Salvia* plants from Central and South America, Western and Eastern Asia, and South Europe and North Africa (Mediterranean) were achieved, since such regions are described as geographical zones for native and endemic plants [17, 18]. Thus, the statistical study included *S. dugesii*, *S. gesneriiflora*, *S. angulata* (America); *S. argentea*, *S. viridis*, and *S. lavandulifolia* (Europe); *S. officinalis, S. africana-lutea*, and *S. chamelaeagnea* (Africa); and *S. miltiorrhiza*, *S. sclarea* and *S. plebeia* (Asia), which were randomly selected to increase the generalizability of the results. Data were correlated, considering individual components, and its respective of structural skeleton. The analyses of essential oils data using multivariate methods were carried out and complemented with univariate analysis, aimed to study intraspecific variations, and identify the most abundant compounds in the species. A principal component analysis (PCA) revealed to chemical correlations found herein. The metabolic analyses suggested a closely chemical similarity between American and Asian species, as well as the close correlation between African and European species.

2. Materials and Methods

2.1. Plant Material

Specimens of *Salvia dugesii* Fernald and *S. gesneriiflora* Lindl. *&* Paxton were collected on April, 2017, at the state of Michoacán, Mexico, N 19°54'24'', W 101°46'17'' at 2049 m above the sea level, and N 19°38'60'', W 102°15'21'' at 2370 m above the sea level, respectively. Specimens of each species (Herbarium numbers: 257299 and 257298, respectively) were deposited at the Herbarium of Instituto de Ecología, A. C., Centro Regional del Bajío, Pátzcuaro, Michoacán, Mexico. Fresh leaves (100 g) of *S. dugesii* or *S. gesneriiflora* were steam distilled for 4 h in 1 L of water in a Clevenger apparatus.

2.2. Analysis of Essential Oils from S. dugesii and S. gesneriiflora

The essential oils of *Salvia dugesii and S. gesneriiflora* were individually analyzed by gas chromatography-mass spectrometry (GC-MS) using a Thermo Scientific GC TRACE 1310 EM ISQ LT apparatus, operated in EI mode (70 eV), equipped with split/splitless injector (250 ºC), using a TG-SQC Thermo Scientific capillary column [15 m x 0.25 mm (i.d.), film thickness: 0.25 μm]. The temperature for the TG-SQC column was 50 °C (5 min) to 250 °C at a rate of 20 °C/min. Helium was used as a carrier gas at a flow rate of 1 mL/min. The identification of the components was based on comparison of their mass spectra with those reported in the database NIST MS Search 2.0 (National Institute of Standards and Technology Mass Spectral Database) and/or by comparison of their relative retention index (RRI) to a series of *n*-alkanes. Alkanes were used as reference points in the calculation of relative retention indices (RRI). Relative percentage amounts of the identified components were calculated from FID chromatograms.

2.3 Multivariate Analysis of Essential Oil Composition from the Species

Essential oil data from twelve *Salvia* plants were used for metabolic correlation, where reported data from ten plants were pooled with the experimental data from *S. dugesii* and *S. gesneriiflora*. The selected plants from literature are natives from the Americas, Asia, Europe, or Africa. The essential oils and structural skeleton matrices were standardized by mean and standard deviation prior to multivariate analysis, and those with percentage abundance below 0.5 were excluded to diminish the error probability during the application of the multivariate models [19, 20]. A total of 146 essential oil components were analyzed (see Table S1) and classified into 29 groups (see Table S2), according their structural skeletons (Figure 1). Matrices of essential oil components and structural skeleton data were individually built according to the Euclidean distance similarities [19]. Then, the data were treated with unsupervised statistical tools to achieve exploratory analyses aimed to establish internal data structures. Metabolic pathways from *Salvia* plants were analyzed by hierarchical clustering algorithm, while data compression was done by principal component analysis (PCA) [21]. All the statistical evaluations were achieved using the Rstudio software v 3.5.1, with statistical significance p ≤ 0.05.

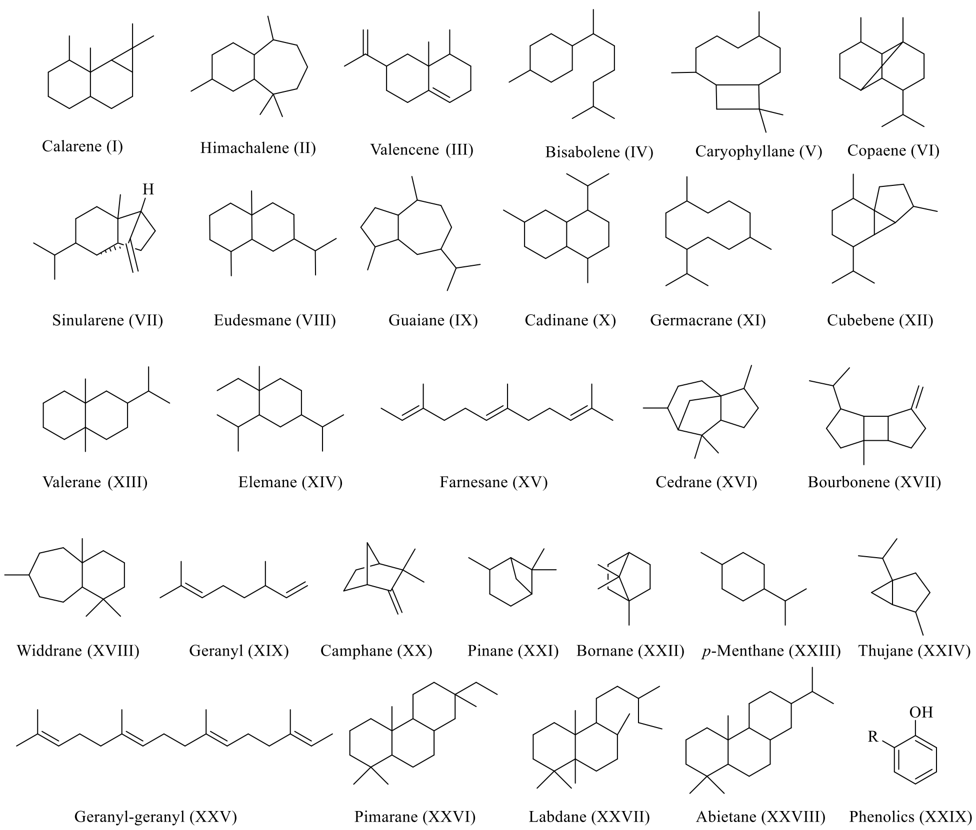

Figure 1. Structural skeletons of essential oil components described in the analyzed *Salvia* species

3. Results and Discussion

Essential oil distillation of *Salvia dugesii* and *S. gesneriiflora* yielded 0.08% and 0.07%, and their chemical compositions revealed the presence of 27 and 25 compounds as main components (Table 1), respectively. Caryophyllene (**8**) highlighted as the most abundant component in essential oils from both studied plants, thereby, the typical chemotype for essential oils from the genus, which is in agreement with the chemotaxonomy of the genus [5, 22]. Bornyl acetate (**6**), valeranone (**30**), together with monocyclic geranyl-α-terpinene (**16**), and hedycaryol (**19**), showed relative concentrations over 5% in *S. gesneriiflora*, which is a native species in Mexico, and its traditional usage is related with gastrointestinal disorders [23]. Bicyclic compounds, including spathulenol (**1**), caryophyllene oxide (**9**), and γ-muurolene (**43**) appeared in *S. dugesii* in percentages as above and abundance of the rest of essential oils constituents is summarized in Table 1. By its part, *S. tiliifolia*, a plant introduced in China in the 1990s, was previously studied but reported as *S. dugesii* [24, 25], leading to confusion. Later, in 2013, such misidentification was corrected [26]. Thus, the first report on chemical study of the American natives *S. dugesii* and *S. gesneriiflora* is herein described.

The above led to questions about chemical similarities between representative *Salvia* species from different geographic zones around the world, particularly to the essential oil composition, since its applications in medicine, scientific research, and industry highlight [27-30]. Therefore, the interest to determine metabolic correlations between representative *Salvia* species in the world to approach rational applications emerged, however, only genetic strategies are described to accomplish this aim [31], which requires samples with specific conditions of collecting and storage, and sophisticate equipment. Consequently, a facile and alternative method becomes pertinent, thus, statistical protocols to approach metabolic similarities were considered, since its use to these approaches are not described for *Salvia* species. Thus, the essential oils compositions of the American *S. dugesii* and *S. gesneriiflora* were pooled and compared with essential oil composition reports of native *Salvia* plants from four continents. A total of twelve plants were considered in the study to give an overview of metabolic correlations of them. Thus, the anti-inflammatory *S. angulata* [32,33] complemented the American representative plants. From Asia, the medicinal plant, Chinese *S. miltiorrhiza* [34-36], the larvicidal *S. plebeia* [37], and the commercial species *S. sclarea* [38] were selected. From Europe, the hemostatic [39] and Spanish specie [40] *S. argentea* [41], the antiseptic *S. viridis* [42], and the sedative [43] *S. lavandulifolia* [44] were considered. Finally, the flu natural medicines [45] *S. africana-lutea*, and *S. chamelaeagnea* [14], as well as the culinary herb *S. officinalis* [46], as representative African *Salvia* species were selected. It is good to mention that several of these species also growing in other representative growing zones [17,18]. 146 essential oil components were herein considered, as depicted Table S1, and all constituents were classified into 29 structural skeletons (Figure 1 and Table S2).

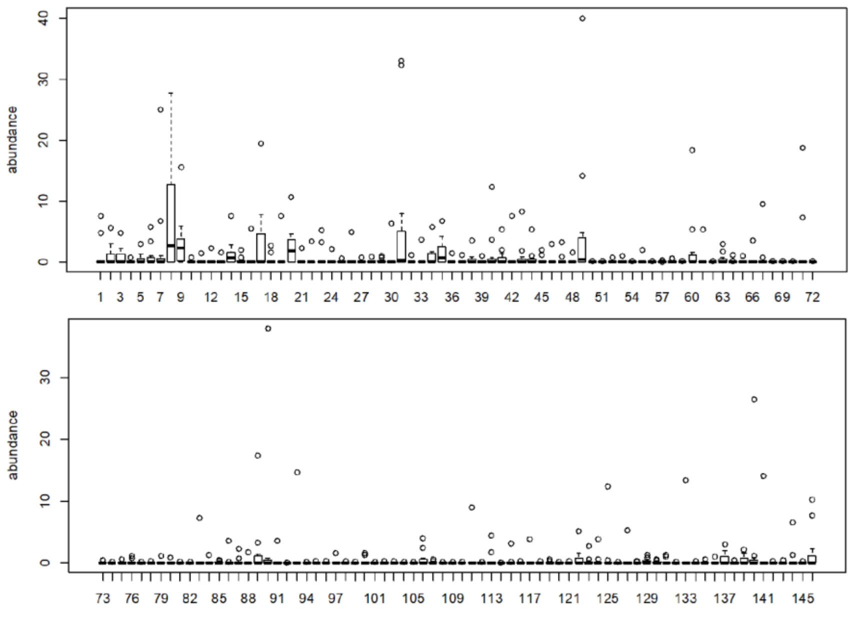

Figure 2. Box-plot diagram of distribution and abundance of the essential oil components from the analyzed *Salvia* species. The thick horizontal line from each data represents the median of the distribution. Boxes include 50% of the data, and the whiskers reach the highest and lowest value within 95% of the distribution. Circles represent single values outside 95% of the distribution

Table 1. Chemical composition of essential oils of *S. dugesii* and *S. gesneriiflora*

Number	RRI	RRI range	Compound	Structural skeleton	Composition (%)	
					S. dugesii	*S. gesneriiflora*
1	1573	1549-1580[a]	Spathulenol	IX	7.63	4.74
2	1382	1366-1398[a]	β-Bourbonene	XVII	1.60	1.01
3	1518	1498-1531[a]	δ-Cadinene	X	4.80	
4	1532	1538[b]	9-Methoxy calamenene	X	0.73	
5	1449	1413-1463[a]	Aromadendrene	X	2.95	1.09
6	1265	1259-1284[a]	Bornyl acetate	XXII	3.35	5.80
7	1139	1106-1153[a]	Camphor	XXII		1.00
8	1389	1384-1430[a]	Caryophyllene	V	10.04	15.68
9	1579	1563-1595[a]	Caryophyllene oxide	V	5.84	2.54
10	1116	115-1138[a]	*cis*-1-Methyl-4-(1-methylethyl)-2-cyclohexen-1-ol	XXIII		0.73
11	1426	1428-1458[a]	*cis*-β-Farnesene	XV	1.47	
12	1561	1551[d]	Diepicedrene-1-oxide	XVI	2.24	
13	1319	1322-1381[a]	Elixene	XIV		1.59
14	1219	1134-1172[a]	*endo*-Borneol	XXII	1.06	1.40
15	1359	1323-1372[a]	Eugenol	XXIX		1.96
16	1922	1902[c]	Geranyl-α-terpinene	XXV		5.49
17	1489	1458-1491[a]	Germacrene D	XI	4.97	
18	1581	1576-1603[a]	Guaiol	IX		2.73
19	1556	1546[e]	Hedycaryol	XI		7.57
20	1438	1430-1436[a]	Humulene	V	4.62	
21	1642	1646[f]	Isoalloaromadendrene epoxide	IX	2.23	
22	1632	1639[e]	Isoaromadendrene epoxide	IX	3.38	
23	1594	1545-1601[a]	Ledol	IX		3.20
24	1122	1100-1129[a]	Phenyl ethyl alcohol	XXIX		2.06
25	2281	2279[g]	Podocarp-7-en-3-one,13β-methyl-13-vinyl	XXVI	0.62	
26	1954	1968[e]	Sandaracopimaradiene	XXVI	4.89	
27	1835	1831[h]	Rimuene	XXVI	0.65	
28	1902	1910[i]	Sclareol oxide	XXVII	0.84	
29	1169	1148-1180[a]	Terpinen-4-ol	XXIII		1.06
30	1647	1633-1668[a]	Valeranone	XIII		6.26
31	1591	1561-1598[a]	Viridiflorol	IX	0.81	
32	1415	1389-1436[a]	α-Cedrene	XVI	1.13	
33	1535	1539[e]	α-Copaen-11-ol	VI		3.66
34	1391	1360-1392[a]	α-Copaene	VI	1.74	
35	949	924-951[a]	α-Pinene	XXI		1.45
36	1495	1485-1511[a]	β-Bisabolene	IV	1.48	
37	1518	1506-1542[a]	β-Cadinene	X		1.20
38	1394	1370-1394[a]	β-Cubebene	XII	0.81	3.56
39	1498	1463-1498[a]	β-Eudesmane	VIII	0.95	
40	1661	1662[e]	7-*epi*-α-Eudesmol	VIII		3.66
41	1507	1490-1521[a]	γ-Cadinene	X	1.39	
42	1484	1418-1499[a]	γ-Elemene	XIV		7.54
43	1478	1455-1494[a]	γ-Muurolene	X	8.31	
44	1037	1035-1062[a]	γ-Terpinene	XXIII		1.03

References in table: a: [47], b: [48], c: [49], d: [50], e: [51], f: [52], g: [53], h: [54], I: [55]

To assess similarities in essential oils compositions, resulted data were firstly examined by box-plot diagrams considering the abundance of each component (Figure 2) and structural skeleton

(Figure 3). As seen in Figure 2, compounds **8**, **9**, germacrene D (**17**), viridiflorol (**31**), 1,8-cineole (**49**), and *α*-pinene (**35**) determined as the most abundant components of the essential oils, thus we can clearly claim that the skeletons caryophyllane (V), guaiane (IX), germacrene (XI) and *p*-menthane (XXIII) were the dominant structural skeletons (Figure 3) for the species, allowing correspondence between both analyses criteria. According to those investigations on the analyzed plants, monoterpene and sesquiterpene pathways are found to be dominant in essential oil biosynthesis, independently from its geographical origin of the species.

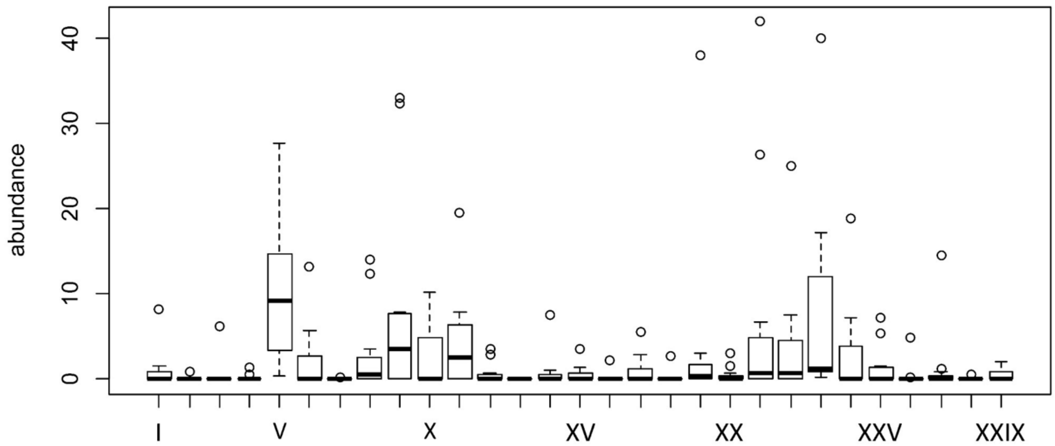

Figure 3. Box-plot diagram of distribution and abundance of the structural skeletons from the analyzed *Salvia* plants. The thick horizontal line from each data represents the median of the distribution. Boxes include 50% of the data, and the whiskers reach the highest and lowest value within 95% of the distribution. Circles represent single values outside 95% of the distribution

A further analysis for evaluation of *Salvia* essential oil metabolism was achieved by a dendrogram study, considering the abundance of structural skeletons (Figure 4). According to Euclidean distances, four similarity clusters were revealed. Cluster composed by V and XI revealed a particular high active metabolism on farnesyl diphosphate derivatives, thereby, sesquiterpene compounds. Important activity for monoterpene biosynthesis is also revealed by cluster conformed by XXI-XXIII. Interestingly, a cluster constituted by IX and camphane (XX) appeared, suggesting the importance of these bicyclic monoterpenes and sesquiterpenes in genus. A more diverse cluster engaged the rest of structural skeletons, which lead to relate the metabolic closeness between monoterpenes and diterpenes, since they come from dimethylallyl diphosphate and isopentenyl diphosphate precursors.

In addition, metabolic connections in each cluster were plausible, where structural skeleton V showed near correspondence with XI, which is comprehensible since they come from the same metabolic precursor by nucleophilic cyclization processes [56, 57]. Further correspondences on several structural skeletons were detected and also associated to direct metabolic pathways connections, which involve carbocation neutralization for subsequent structural diversification, a typical property in essential oil compositions, and including valencene (III) and valerane (XIII); geranyl-geranyl (XXV) and pimarane (XXVI); bisabolene (IV) and farnesane (XV); pinane (XXI) and XXIII; and XX and bornane (XXII). Moreover, dendrogram from Figure 4 suggested a concentration-dependent process of XXI or XXII biogenesis from XXIII.

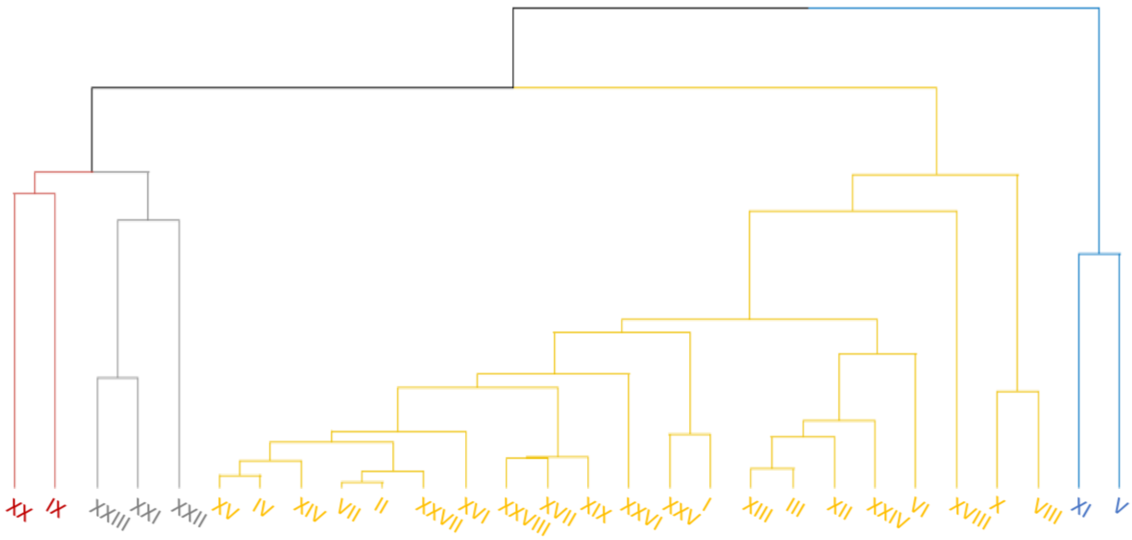

Figure 4. Dendrogram of metabolic correlation between the twelve analyzed *Salvia* plants, according to the structural skeletons of essential oils components

Interesting metabolic disconnections were also observed by highlighting the poor correspondence between XI and IX, despite XI is directly associated to metabolism of IX through standard reactions of carbocations [58]. In addition, the bicyclo[4.4.0]decane VIII and bicyclo[5.3.0]decane IX concentrations are not dependent each other, despite they are synthesized from the same metabolic precursor (XI). These results are in concordance with thermodynamic data related with reactivity and stability of intermediates, transition states and reaction products from sesquiterpene biogenesis, due to described strain energies associated to carbocyclic rings for cyclohexane and cyclopentane are approximately 7 kcal/mol [59]. The above-mentioned issues clearly shows that XI is a strategic metabolic intermediary for sesquiterpene diversification in *Salvia* essential oils, allowing knowledge on key biosynthetic processes for future physiological or biotechnological purposes.

After metabolic scrutiny, data compression by principal component analysis (PCA) was achieved (Figure 5). The similarities of the studied species considering the structural skeletons data provided an explanation of 48.3% (Figure 5a), where two *Salvia* blocks appeared. Each block is characterized by the preference for C_{10} or C_{15} terpenoids biogenesis. The first block is constituted by American-Asian plants, including *S. dugesii* and *S. gesneriiflora*, whose biogenesis tended to V/XI compounds is well defined. Macrocyclic XI is formed directly by cyclization between C1 and C10 from farnesyl cation, and further cyclization can lead to bicyclic skeletons such as VIII and IX, while precursor of V involves an anti-Markovnikov ring closure between C1 and C11, thus humulene skeleton. Interestingly, this structural skeleton is not present in higher concentrations in analyzed *Salvia* plants, suggesting that humulyl cation preferably is transformed to V, which can be associated to the lower thermodynamic stability of the macrocyclic intermediary since a secondary carbocation is required in the last pathway to form V [59].

The second block contains African-European species, and biogenesis of these plants tends to 2.2.1 bicyclic compounds formation (XX and XXII), which come from XXIII. Biogenesis of XXII requires bornyl cation formation which is stabilized by functionalization or Wagner-Meerwein rearrangement [60]. If the last chemical process occurs, XX is formed, consequently, the above possibilities seem to have the same chance in *Salvia* from this block. The case of the Turkish *S. argentea* and S. *africana-lutea* are slightly separated from its block, however, biogenesis of XXI highlighted for these *Salvia* species as well. In addition, its metabolic tendency to VIII and IX compounds appeared, suggesting these skeletons biogenesis as preferred over that for V in farnesyl diphosphate pathways.

Data compression from individual essential oil components analysis (Figure 5b) suggested **8**/**17** for American-Asian plants as the representative compounds, and **31**/**49** for African-European species, consequently, nature of volatile compounds is dominant according to the geographical zone.

Interestingly, the European *S. viridis*, and the Asian *S. plebeia* appeared in the American-Asian species block with poorly correlation as observed in Figure 5b, surely related with its diversification on secondary metabolites, but tended to biogenesis of **17**. In addition, biogenesis of compounds **1**, **9**, **43**, **60** and **90** is deeply related with that for dominant sesquiterpene (**17**) in American-Asian block, suggesting the presence of these sesquiterpene compounds are related with biochemical particularities of each plant from the block. In case of African-European plants group, the dispersion of compounds **7**, **35**, **71**, **89** and **93** in PCA depicts a higher influence in *S. chamelaeagnea* than that for the rest of plant in this segment, however, the monoterpenic nature of compounds supports the established classification for *Salvia*. The explained variances were 40.1%, suggesting good representation on *Salvia* metabolism, now, with specific metabolites, their concordance with PCA results from structural skeleton provided confidence and validation of the analyses criteria. As seen, interconnections on metabolic pathways from *Salvia* plants and its geographical zone growth are revealed, thus, complete environmental adaptivity of *Salvia* plant from America-Asia can be associated to sesquiterpene biogenesis preferences, while European-African species must be represented by monoterpene pathways dominance.

These results are in harmony with phylogenetic studies of angiosperms from America and Asia, where molecular evolutive approaches were described [61]. In the same context, African and European *Salvia* plant similarities are consistent with recent genetic studies [31], suggesting the present essential oil metabolism scrutiny as a suitable tool for *Salvia* metabolic correlations, and beyond this scientific finding, a direct sight of their potential applications. Thus, American-Asian *Salvia* species could share applications aimed to counter several diseases, including inflammation, microbial infection, among others, and to gain commercial importance as that for *S. sclarea*, which is employed in preparation of medicines against respiratory diseases in Europe. On the other hand, African-European plants for cosmetic or food applications as that well-known for *S. officinalis* can be prominent. Moreover, such *Salvia* plants block, as nutraceuticals could be considered due to its importance as flu natural medicines, hemostatic, or antiseptic components.

4. Conclusion

The current study of *S. dugesii* and *S. gesneriiflora* showed the chemical similarities against the rest of American-Asian plants herein analyzed. These *Salvia* species revealed preferences for the sesquiterpene metabolism for its essential oil composition, highlighting caryophyllene skeleton as the most important class of terpenoid. Multivariate methods, complemented with univariate analysis using the essential oil components from *Salvia* plants from four continents were able to reveal rational evidence about two *Salvia* plant blocks, American-Asian and African-European, thereby, metabolic preferences on terpenoid biosynthesis according to native growth zones. The above represents a suitable and accessible tool for taxonomic approaches for *Salvia* genus. As seen, the recent studied *Salvia* species matched in the analyses, and potential applications, according to literature, can be sight in the present analysis, e.g., natural medicines, nutraceutical ingredients, natural molecular gastronomy supplies, or its arrival as exotic scents in commercial products can be also suggested.

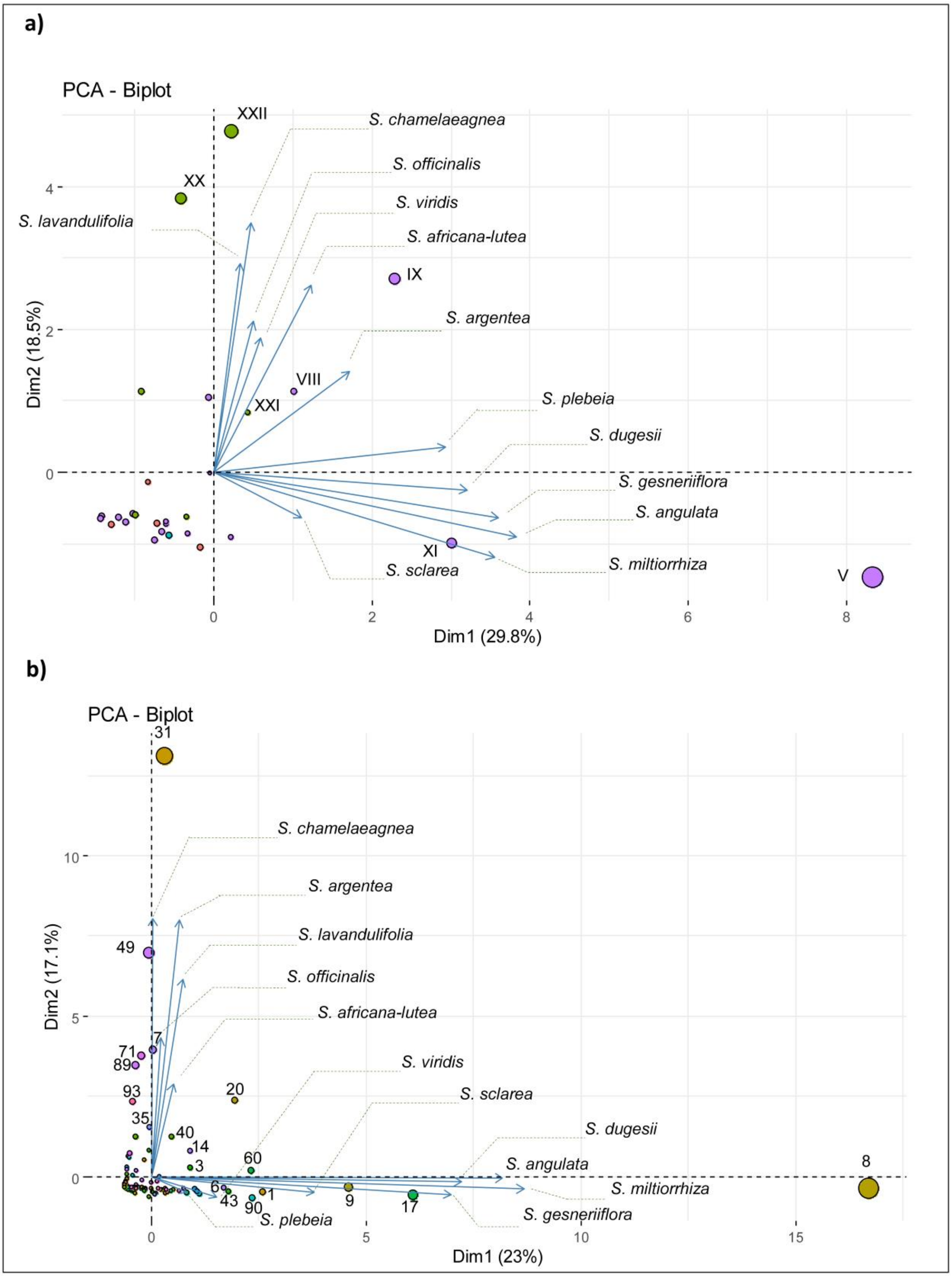

Figure 5. Principal component analysis of essential oils from *Salvia* plants, **a**) employing structural skeleton abundance data, and **b**) considering the individual components

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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