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Original Article

Chemical compositions of *Sideritis albiflora* Hub. – Mor.

Damla Kırcı[1,2], Nagehan Saltan[3], Fatih Göger[4], Yavuz Bülent Köse[3], Betül Demirci[4]

[1]Selçuk University, Faculty of Pharmacy, Department of Pharmacognosy, Konya, Turkey
[2]Anadolu University, Graduate School of Health Sciences, Eskişehir, Turkey
[3]Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Botany, Eskisehir, Turkey
[4]Anadolu University, Faculty of Pharmacy, Department of Pharmacognosy, Eskisehir, Turkey

ORCID IDs of the authors: D.K. 0000-0002-9881-164X; N.S. 0000-0002-1207-909X; F.G. 0000-0002-9665-0256; Y.B.K. 0000-0002-3060-7271; B.D. 0000-0003-2343-746X

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ABSTRACT

Background and Aims: *Sideritis* species (Lamiaceae) which are quite widespread in the Mediterranean region and represented by 46 species and 53 taxa in Turkey, are often used as a antirheumatic, anti-inflammatory, antimicrobial and diuretic remedies.
Methods: In this study, the infusion (INF), essential oil (EO) and methanolic extract (ME) of chemical compounds prepared from aerial parts of *Sideritis albiflora* Hub.-Mor. (endemic) were investigated.
Results: The presence of chlorogenic acid, verbascoside, forsythoside, apigenin glucoside, and isoscutellarein derivatives in the infusion and methanol extract of the plant was determined by LC-MS / MS analysis. In addition, the main constituents of the essential oil were found as germacrene D (23.5%), *ß*-caryophyllene (13.6%) and caryophylene oxide (8.0%) by GC / MS and GC / FID simultaneously.
Conclusion: In this study, the essential oil, the methanolic extract and the infusion of S. albiflora species were prepared and their chemical compositions elucidated. It was determined that the essential oil chemical compound composition is rich in terms of the sesquiterpene group.
Infusions of aerial parts of some *Sideritis* species have traditionally been used in the treatment of many diseases. Accordingly, the fact that the phenolic compounds of *S. albiflora* infusion have not been studied before increases the importance of this study. In addition, the therapeutic effect was shown to be related to major *S. albiflora* compounds, and the correlation between *in vitro* activity and ethnobotanical use was evaluated. The effective phenolic compounds contained in *S. albiflora* are thought to support the traditional uses of the plant.

Keywords: *Sideritis albiflora*, infusion, polyphenolic compounds, methanolic extract, essential oil

INTRODUCTION

There are over 10,000 species of wild flowering plants in Turkey and one third of them are aromatic (Karahüseyin & Sarı, 2019). The consumption of herbal tea prepared from wild plants is very common, especially in rural areas, and one of the most used herbs asherbal tea is the *Sideritis* genus, which is generally found in the Aegean and Mediterranean regions. As of the most recent taxonomic classification, *Sideritis* genus includes over 150 species distributed in the Western Palearctic region. Around 90% of all *Sideritis* species are found in Turkey, with around 80% of them being endemic to the country (Aneva, et al., 2019). *Sideritis* (*Lamiaceae*) species are represented in Turkey by 46 species and 53 taxa, 39 of which are endemic (Kirimer, Tabanca, Özek, Tümen, & Baser, 2000).

Sideritis species are generally known as "Dağ çayı" in the regions where they grow in Turkey. Infusions of aerial parts of some species of *Sideritis* are used as diuretic, anti-inflammatory agent, antispasmodic remedyies, and as a carminative tonic. In ad-

Address for Correspondence:
Damla KIRCI, e-mail: damlakirci93bnd@gmail.com

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dition, they are used in the treatment of colds and digestion (Ezer, Vila, Canigueral, & Adzet, 1996; Yeşilada, & Ezer, 1989).In addition, *Sideritis* species, which are common in our country, are poor in diterpenes, phenylethanoid glycosides, flavonoids and essential oils. *Sideritis albiflora* Hub.- Mor, belonging to the section *Empedoclia*, is endemic in Turkey and, locally known as "Akçiçek çayı, Yayla çayı, Bozlan çayı" (Guner, Aslan, Ekim, Vural, & Babaç, 2012; Türkmenoğlu, & Duman, 2015) . In folk medicine, herbal tea prepared from inflorescence and leaves is used as an antimicrobial, anti-inflammatory, analgesic, nerve stimulative, sedative, antitussive, anticonvulsant, antispasmodic, carminative, and cold and cough suppressant. It is also used in the treatment of digestive system diseases (González-Burgos, Carretero, & Gómez-Serranillos, 2011; Türkmenoğlu, & Duman, 2015; Sarac, & Ugur, 2007).

While over 15 *Sideritis* species have been investigated for their non-volatile components in studies to date, about 50 *Sideritis* species have been investigated for their essential oil compositions, and most of these have been reported to contain *α* or *β*-pinene or both (Topçu et al., 2008; Deveci, Tel-Çayan, Usluer, & Duru, 2019a). *Sideritis* essential oils were classified by Başer and Kırımer according to their main components, and *S. albiflora* was included in those rich in sesquiterpenes and it was reported that the main component was *β*-caryophyllene (Başer, & Kırımer, 2018). Although *Sideritis* species are poor in essential oil, they have a pleasant aroma and fragrance (Kirimer, Baser, Demirci, & Duman, 2004; Deveci et al., 2019a).

Since the compounds with polyphenolic structure have important biological activities, it is necessary to determine their presence in plants. Rosmarinic acid, carvacrol, caffeic acid, apigenin, luteoline were detected in the methanol extract of *S. albiflora* by Askun et al, 2009. In a study by Deveci et al., 2019, Rosmarinic acid and caffeic acid were identified as the most abundant phenolic compounds, and acetone extract of *S. albiflora* was found to be the best reducing agent in the copper reducing antioxidant capacity (CUPRAC) test (Askun, Tumen, Satil, & Ates, 2009; Deveci, et al., 2019a).

Owing to the importance of the genus *Sideritis* in herbal remedies, it is necessary to investigate its chemical compounds and its biological activities in detail. This study aimed to elucidate the chemical compositions of the volatile and non-volatile compounds of *S. albiflora,* which is traditionally used in the treatment of many diseases in Turkey.

Therefore, in this study, the chemical composition of methanolic extract (ME), essential oil (EO) and infusion (INF) of *Sideritis albiflora*, an endemic species, was investigated by GC-MS and GC-FID, LC-MS/MS. Thus, the relationship between their chemical composition and biological effect has been elucidated.

MATERIAL AND METHODS

Plant material and essential oil (EO)

*The aerial parts of S. albiflora were collected in July 2018 from Muğla, Turkey. The plant material was diagnosed by Dr. Y. B. Köse and voucher specimens are kept at the Herbarium of the Faculty of Pharmacy of Anadolu University in Eskisehir, Turkey (*ESSE 15497).

The EO was obtained by hydrodistillation using a Clevenger type apparatus for 3h. The yield of S. albiflora herba was 0.07% on moisture-free basis and the oil was analyzed by GC-FID and GC-MS, simultaneously.

Infusion and methanol extract

The dried aerial parts of S. albiflora were weighed to prepare 10% of the infusion extract. The sample was added to boiled water at 70-80 °C. Then it was brewed for 10 minutes. Infusion extract was lyophilized in a freeze dryer (FreeZone 2.5 Liter Benchtop Freeze Dryer, Labconco) after it was analyzed for non-volatile compounds with LC-MS/MS.

To prepare a methanolic extract of S. albiflora aerial parts, 10g of the aerial parts were weighed and powdered. The plant material was put through maceration process for 48 hours in a dark container at room temperature and then filtered. This process was repeated, after which the two methanolic extracts obtained because of the process were combined and evaporated to dryness using an evaporator and then stored at -20°C.

Essential oil composition with GC-MS and GC-FID methods

The hydrodistilled essential oil of S. albiflora was analyzed by GC-MS and GC-FID (Demirci et al., 2019). The results of the analyses are given in Table 1.

*Identification of the essential oil compounds was performed by comparison of their relative retention indices (RRI) with those of authentic samples. Computer matching against commercial (MassFinder 3 Library, Wiley GC-MS Library) (Tabanca et al., 2014) and in-house "Başer Library of Essential Oil Constituents" built up by genuine compounds of known essential oils, as well as MS published in the literature (*Joulain, & Koenig, 1998; ESO, 2000) *were used for the identification.*

LC-MS/MS analysis

LC-MS/MS analysis of the methanolic extract of Sideritis albiflora was assessed using a previously described process (Gürbüz et al., 2019). LC-ESI-MS/MS data were collected and processed by Analyst 1.6 software.

RESULTS AND DISCUSSION

Extraction yield and composition of essential oil

The aerial parts of *S. albiflora* were subjected to Clevenger type apparatus to obtain the EO and the EOyield was found to be 0.07%. While *Sideritis* is a member of the *Lamiaceae* family, it does not contain much essential oils (Żyżelewicz, Kulbat-Warycha, Oracz, & Żyżelewicz, 2020).

The EO was analyzed by both GC-FID and GC-MS, simultaneously. 88 compounds representing 88.2% of the EO was characterized with germacrene D (23.5%), *β*-caryophyllene (13.6%), caryophyllene oxide (8.0%) and hexadecanoic acid (3.8%) as major constituents. The results are given Table 1.

Terpenoids are included in the major class of natural components, with a few thousands known compounds. The terpenoids that are originated from plant and marine organisms are classified as monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes and meroterpenes (Gozari, Alborz,

Table 1. The Composition of the Essential Oil of *Sideritis albiflora*.

RRI	Compound	%
1032	α-Pinene	2.0
1035	α-Thujene	0.1
1118	β-Pinene	3.5
1132	Sabinene	0.1
1151	δ-3-Carene	0.1
1174	Myrcene	0.1
1176	α-Phellandrene	0.1
1203	Limonene	1.8
1218	β-Phellandrene	1.0
1225	*(Z)*-3-Hexenal	0.2
1244	2-Pentyl furan	0.1
1255	γ-Terpinene	0.1
1280	*p*-Cymene	tr
1290	Terpinolene	tr
1400	Nonanal	1.0
1452	1-Octen-3-ol	0.4
1466	α-Cubebene	tr
1495	Bicycloelemene	tr
1497	α-Copaene	0.5
1506	Decanal	0.2
1528	α-Bourbonone	0.1
1535	β-Bourbonone	1.3
1553	Linalool	0.2
1572	α-Bergamotene	0.1
1583	Longifolene (=*Junipene*)	0.1
1586	Pinocarvone	0.2
1589	β-Ylangene	0.2
1597	β-Copaene	0.2
1600	β-Elemene	0.3
1612	β-Caryophyllene	13.6
1638	β-Cyclocitral	0.1
1648	Myrtenal	0.2
1655	*(E)*-2-Decenal	0.2
1661	Alloaromadendrene	0.1
1668	*(Z)*-β-Farnesene	0.1
1670	*trans*-Pinocarveol	0.3
1683	*trans*-Verbenol	0.3
1687	α-Humulene	0.8
1704	γ-Muurolene	0.3
1706	α-Terpineol	0.3
1726	Germacrene D	23.5
1740	α-Muurolene	0.2
1755	Bicyclogermacrene	2.6
1758	*(E,E)*-α-Farnesene	tr
1764	*(E)*-2-Undecenal	0.2
1773	δ-Cadinene	0.1
1776	γ- Cadinene	0.9
1784	*(E)*-α-Bisabolene	0.1
1785	7-*epi*-α-Selinene	0.3
1804	Myrtenol	0.3
1808	Nerol	0.1
1868	*(E)*-Geranyl acetone	0.2
1945	1,5-Epoxy-salvial-4(14)-ene	0.1
1957	Cubebol	0.1
1958	*(E)*-β-Ionone	0.4
2001	Isocaryophyllene oxide	0.6
2008	Caryophyllene oxide	8.0
2037	Salvial-4(14)-en-1-one	0.3
2050	*(E)*-Nerolidol	0.3
2071	Humulene epoxide II	0.5
2104	Viridiflorol	0.3
2130	Salviadienol	1.3
2131	Hexahydrofarnesyl acetone	1.0
2144	Spathulenol	1.8
2179	3,4-Dimethyl pentyliden-2(5H)-furanone	0.1
2186	Eugenol	0.2
2192	Nonanoic acid	0.1
2202	Germacrene D-4-ol	0.2
2209	*T*-Muurolol	0.3
2214	ar-Turmerol	0.1
2219	Dimyrcene II-a	0.2
2247	*trans*-α-Bergamotol	0.1
2255	α-Cadinol	1.2
2264	Intermedeol	1.0
2312	9-Geranyl-*p*-cymene	0.4
2324	Caryophylladienol II	0.4
2369	Eudesma-4(15)7-dien-1-β-ol	1.3
2380	8α-13-Oxy-14-en-epi-labdane	0.3
2389	Caryophyllenol I	0.3
2392	Caryophyllenol II	0.9
2503	Dodecanoic acid	0.2
2567	14-Hydroxy-α-muurolene	0.1
2607	14-Hydroxy-δ-cadinene	0.3
2622	Phytol	0.4
2670	Tetradecanoic acid	0.4
2700	Heptacosane	0.6
2900	Nonacosane	1.8
2931	Hexadecanoic acid	3.8
	Total	**88.2**

Note: %: calculated from FID data; tr: Trace (<0.1 %)

El-Seedi, & Jassbi, 2020). In this research, the chemical structure of germacrene D, which is determined as one of the major components of the EO of *S. albiflora* herb, is a sesquiterpene and this component constitutes approximately one quarter of the chemical composition of the EO obtained from the plant.

β-Caryophyllene is a sesquiterpene compound with a bicyclic structure. It is found in the content of food and nutrition supply. That compound is very important due to its biological activities such as antiinflammatory, antipruritic, lavricidal, anticolitis, antimicrobial, neuroprotective, gastroprotective and nephroprotective activities. *β*-Caryophyllene is considered to be safe for safe to consuming, due to its low toxicity level, and a wide therapeutic index (Russo & Marcu, 2017).

Caryophyllene oxide, which is a sesquiterpenoid oxide, is commonly included in the plants. It is of great importance due to its insecticidal and broad-spectrum antifungal biological activities and this compound shows antiplatelet aggregation properties. Also, caryophyllene oxide is non-sensitizing and non-toxic (Russo & Marcu, 2017).

Kırımer and co-workers were first to report the main constituents of the essential oil of *S. albiflora* as *β*-caryophyllene (35.0%) (Kirimer, Baser, Demirci, & Duman, 2004). Topçu and co-workers determined *γ*-cadinene (12.8%; 12.1%), *trans*-caryophyllene (14.8%; 17.4%), *β*-pinene (15.4%; 13.5%) and *α*-pinene (16.3%; 15.4%) as major compounds by headspace analysis (Topçu et al., 2008). Deveci et al., 2019 recently identified *β*-caryophyllene (21.2%), palmitic acid (12.3%), *τ* -gurjunene (13.6%), caryophyllene oxide (9.0%), carvacrol (6.0%) and viridiflorol (6.0%), as major components (Deveci et al., 2019a). Carvacrol (24.82%), *β*-caryophyllene (17.32%) and *γ*-elemene (14.13%) were found as major components in the essential oil of *S. albiflora* by Usluer et al., 2005 (Usluer, Duru, & Öztürk, 2005). In the previous studies, *S. albiflora* was collected from Fethiye and Muğla (Topçu et al., 2008; Deveci et al., 2019a). Although the results are compatible with our study, there are also some differences in the quantity and quality of *S. albiflora* essential oils. This can be attributed to the climatic conditions, soils and extraction methods. When *Sideritis* genus is classified according to essential oil compositions, monoterpene hydrocarbons are widely available. *β*-Caryophyllene is the most detected major compound (Başer, & Kırımer, 2018).

Infusion and methanolic extract composition

In LC-MS/MS analysis, chlorogenic acid, verbascoside, forsythoside, apigenin glucoside and isoscutellarein derivatives were determined in the methanolic extract and infusion of the plant. The other *Sideritis* species have also been shown to contain these compounds as main constituents (Jaiswal, Kiprotich, & Kuhnert, 2011; Petreska et al., 2011; Stanoeva et al., 2015; Axiotis, Petrakis, Halabalaki, & Mitakou, 2020; Żyżelewicz et al., 2020). The isoscutellarein derivatives are very characteristic for *Sideritis* species and verified in literature studies (Żyżelewicz et al., 2020). The compounds have phenolic structure and, they have very important biological activities. All of the compounds found in this study have antimicrobial and anti-inflammatory properties (Xing, Peng, Wang, Chen, & Li, 2014; Smiljkovic et al., 2017; Kim, & Park, 2019; Kubica et al., 2020; Żyżelewicz et al., 2020). Traditional use is consistent with the literature studies.

The results are given in Table 2. MS spectra of the identified compounds are given in Figures 1 and 3. Compound 1 showed the molecular ion peak at m/z 353 [M-H]- and base peak at m/z 191 and the small amount product ion at m/z 179. Compound 1 was determined as 5-caffeoylquinic acid (Deveci et al., 2019a; Clifford, Knight, & Kuhnert, 2005) as previously determined in the genus *Sideritis* (Petreska et al., 2011; Stanoeva, Bagashovska, & Stefova, 2012).

The molecular ion peak of Compound 2 was peak at m/z 755 [M-H]- which fragmented to the base peak ion at m/z 593 due to the loss of a caffeoyl unit. A pentose loss was due to m/z 461 (M-H-132). Rhamnose loss was due to the ion at m/z 315 (M-H-132-146). m/z 297 ion was observed due to the loss of H_2O. Caffeic acid related ions at m/z 179, 161 and 135 were also observed. This fragmentation behavior led us to believe that compound 2 is a caffeoyl phenylethanoid glycoside. MS fragmentation agreeing with Forsythoside B was reported by Mitreski and Kırmızıbekmez (Stanoeva et al., 2012; Mitreski et al., 2014; Kırmızıbekmez et al., 2005).

Compound 3 showed the molecular ion peak at m/z 623 [M-H]- which presented fragment ions at m/z 461, 305, 179 and 161. The fragmentation pattern was like that of forsythoside B. Verbascoside was previously identified in several *Sideritis* species. It gives the same fragments, therefore, compound 3 was determined as verbascoside (Petreska et al., 2011; Ah-

Table 2. The phenolic composition of *S. albiflora* ME and INF.

Compound No	Rt	M-H	Base peak	MS^2	Identification
1	7,8	353	191	179	5-Caffeoylquinic acid
2	9,6	755	593	461, 315, 297, 179, 161, 135	Forsythoside B
3	10,1	623	161	461, 315, 179,133	Verbascoside
4	11,2	623	299	461, 284	4'-O-Methylisoscutellarein 7-O-allosyl(1-2) glucoside
5	12,7	431	295	363, 269	Apigenin glucoside
6	13,2	651	285	609, 591, 447, 429, 379	Isoscutellarein 7-O-[6'''-O-acetyl]-allosyl(1-2) glucoside

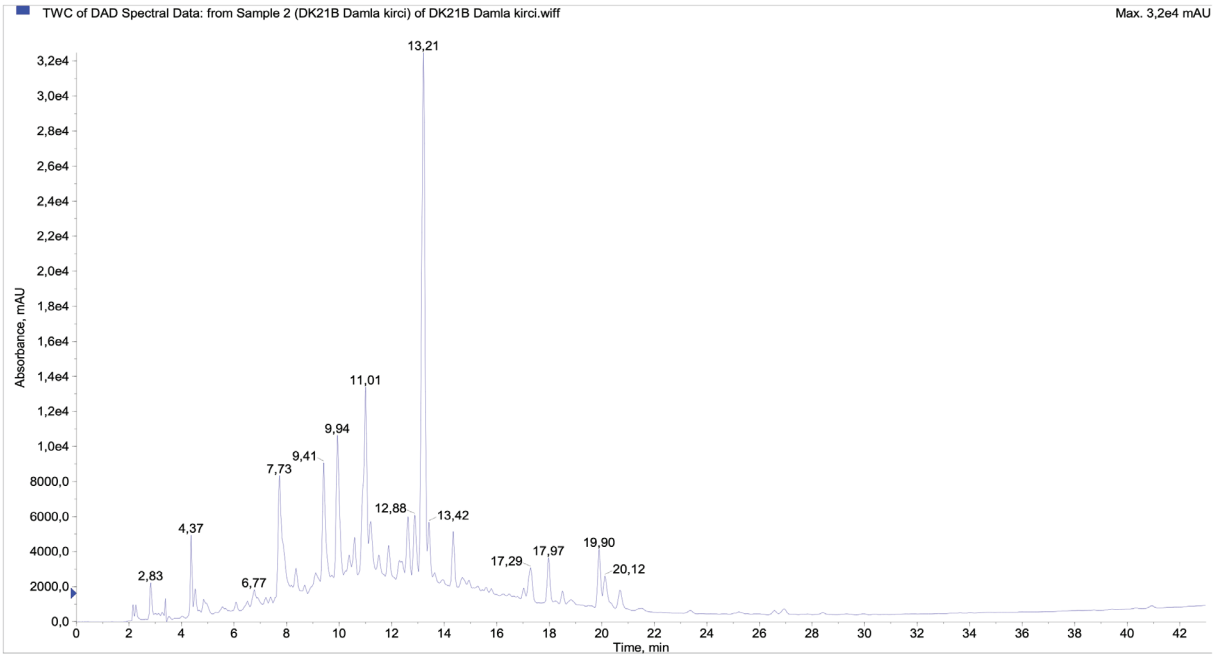

Figure 1. 70% Methanol extract LC-MS/MS.

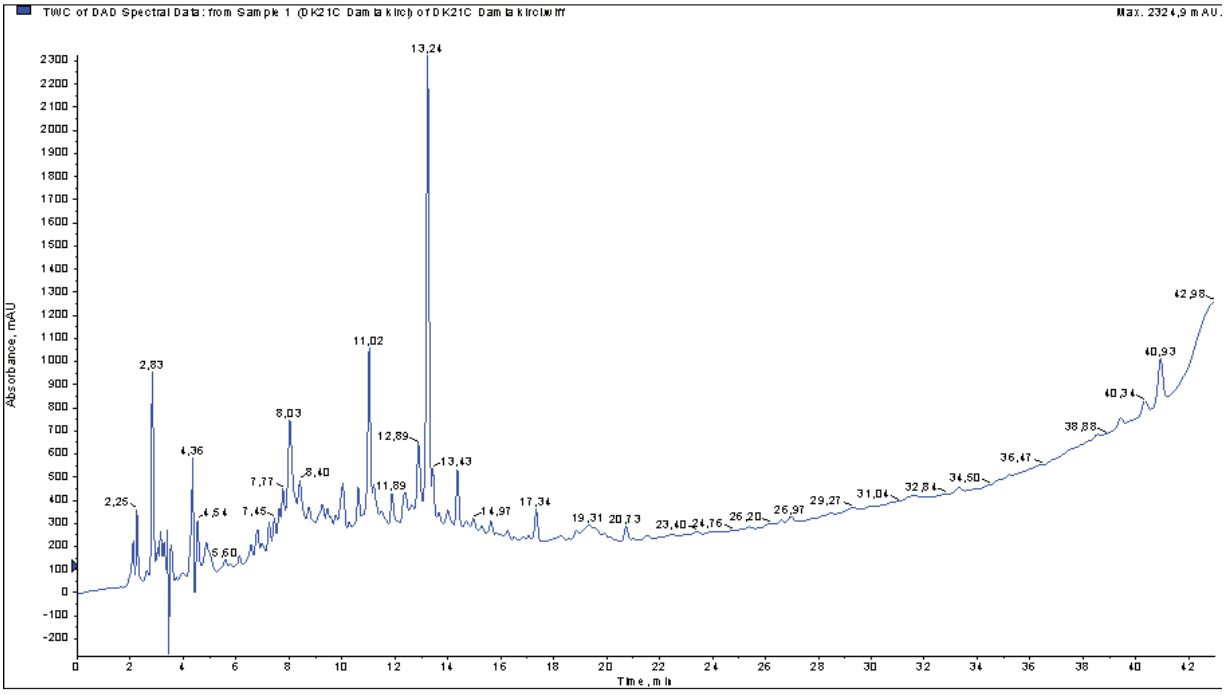

Figure 2. Infusion LC-MS/MS.

mad et al., 2006; Karioti, Bolognesi, Vincieri, & Bilia, 2010; Asnaashari et al., 2010).

Compound 4 showed the molecular ion peak at m/z 623 [M-H]- Ion at m/z 299 was fragmented to m/z 284 due to the weakness of a 15 amu methyl unit. Loss of 324 amu from molecular ion peak indicates a dihexoside of methylisoscutellerain. 366 amu (dihexose +acetyl) indicates that sugar part was acetylated. Methylisoscutellerain is a flavonoid which is found in many *Sideritis* species (Karioti et al., 2010). Compound 4 was therefore characterized as 4'-O-methylisoscutellarein 7-O-allosyl (1→2) glucoside as previously determined in *Sideritis* species (Petreska et al., 2011).

Compound 5 was identified as apigenin glucoside which presented a molecular ion peak at m/z 431 M-H]- and fragmented to base peak ion at m/z 269 (apigenin) after the loss of a glucose unit (-162). Apigenin glucoside and derivatives

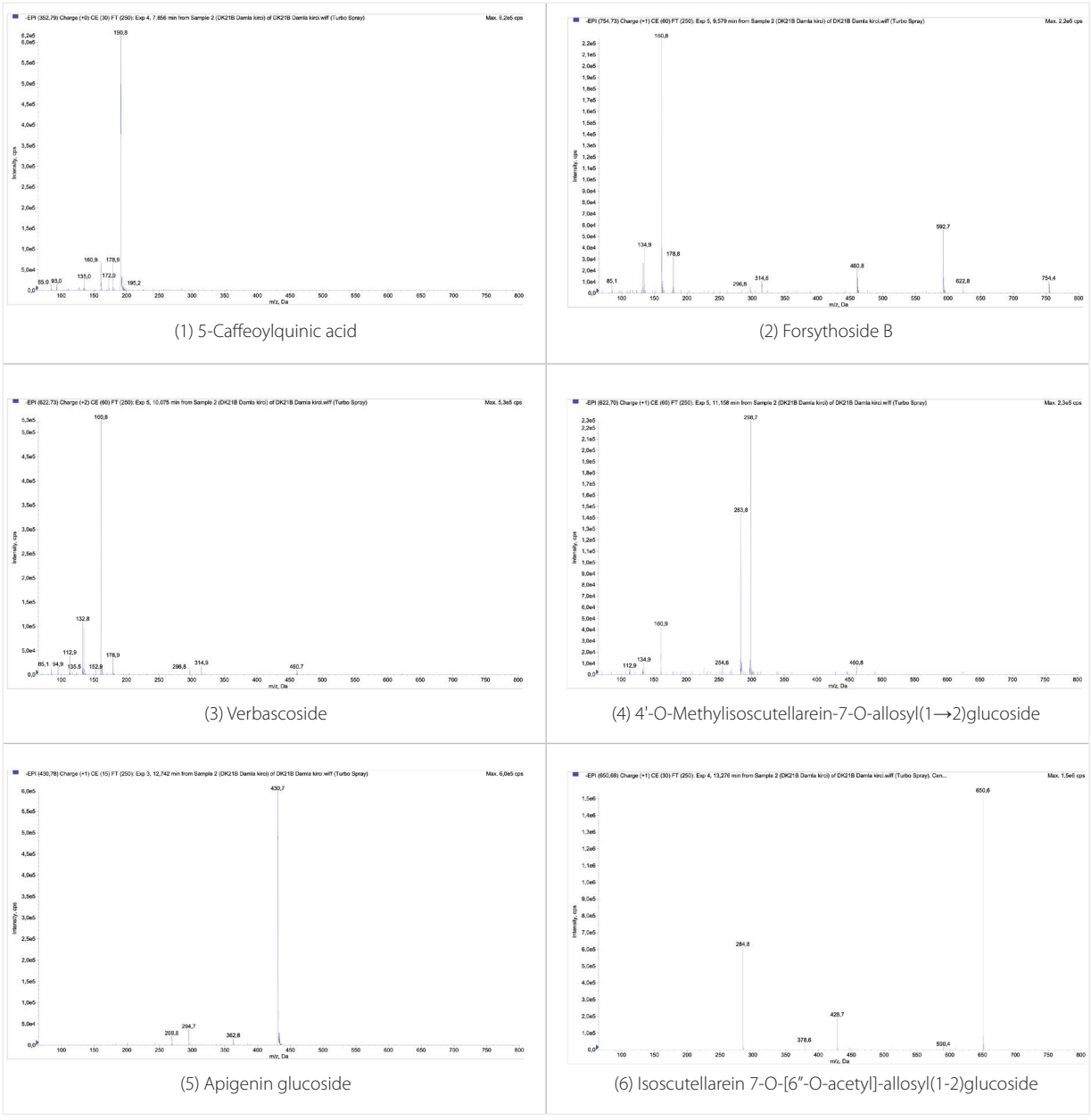

Figure 3. LC-MS/MS analysis of *S. albiflora* ME and INF compounds: (1) 5-Caffeoylquinic acid, (2) Forsythoside B, (3) Verbascoside, (4) 4'-O-Methylisoscutellarein-7-O-allosyl(1→2)glucoside, (8) Apigenin glucoside, (9) Isoscutellarein 7-O-[6"-O-acetyl]-allosyl(1-2)glucoside.

were previously determined in *Sideritis* species (Ulubelen, Topcu, & Kolak, 2005).

Compound 6 showed a [M-H]- ion at m/z 651 and its MS2 spectrum showed a base peak ion at m/z 285 due to the loss of 324 amu, probably a diglucose moiety. The presence of an ion at m/z 429 (M-H-180) indicates that glycosidation occurred in position 1-2 between the sugars (Petreska et al., 2011). Fragmentation behavior of compound 6 was identified as similar to that of isoscutellarin 7-O-allosyl (1-2) glucoside but 42 amu higher molecular ion peak than this compound indicated that compound 6 was an acetylated derivative of this compound, which led us to characterize the compound 6 as isoscutellarein 7-O-[6‴-O-acetyl]-allosyl(1-2) glucoside (Petreska et al., 2011; Pereira, Domingues, Silva, & Cardoso, 2012).

Deveci and co-workers investigated the phenolic compounds of the methanolic extract (ME) of the aerial parts of *S. albiflora* and identified carvacrol and rosmarinic acid (Deveci, Tel-Çayan, Duru, & Öztürk, 2019b). In another study, rosmarinic acid, caffeic acid and carvacrol were found as major phenolic compouns in S. albiflora. . Askun et al. 2009, determined the phenolic compounds of five *Lamiaceae* family members including *S. albiflora* by HPLC (Askun, et al., 2009).They reported that the methanol extract prepared from the aerial parts of *S. albiflora* contained caffeic acid, rosmarinic acid, carvacrol, apigenin, luteolin, naringin and it exhibited antibacterial effect in some Gram posi-

tive and Gram negative bacteria species. In another study, the antioxidant effect of *S. albiflora* aqueous extract was revealed by Güvenç et al. (2005) without reporting the chemical composition of the extract (Güvenç, Houghton, Duman, Coşkun, & Şahin, 2005).

In previous studies, no research was found on the chemical constituents of infusion of the herbal parts of *S albiflora*. Considering the widespread use of the herbal tea of *S. albiflora* species as infusion in our country, a proper determination of the chemical composition of the infusion of this plant was deemed necessary.

CONCLUSIONS

Sideritis genus is widely available in Turkey, which are among it is an important group of medical and economic plants. In this study, essential oil, methanolic extract and infusion of *S. albiflora* species were prepared and their chemical compositions were defined. It has been determined that the essential oil composition is rich in terms of the sesquiterpene group.

Infusions of aerial parts of some *Sideritis* species have traditionally been used in the treatment of many diseases. Accordingly, the fact that the phenolic compounds of *S. albiflora* infusion have not been studied before increases the importance of this study. In addition, in this study, the therapeutic effect was shown to be related to major *S. albiflora* compounds, and the correlation between *in vitro* activity and ethnobotanical use was evaluated. The effective phenolic compounds contained in *S. albiflora* are thought to support the traditional uses of the plant.

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