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PHYTOCHEMICAL ANALYSIS ON THE LEAVES OF *TEUCRIUM CAPITATUM* L. SUBSP. *CAPITATUM* COLLECTED IN THE BOTANICAL GARDEN OF ROME

Frezza C.[1*], De Vita D.[1], Francioni F.[1], Giampaoli O.[1], Dal Bosco C.[2], Sciubba F.[1,3], Bonito A.[1], Attorre F.[1]

[1]*Department of Environmental Biology, Sapienza University of Rome, Italy*
[2]*Department of Chemistry, Sapienza University of Rome, Italy*
[3]*NMR Lab, Sapienza University of Rome, Italy*
** Corresponding Author Email: claudio.frezza@uniroma1.it*

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Abstract – In this paper, the phytochemical study on the leaves of *Teucrium capitatum* L. subsp. *capitatum* collected in the Botanical Garden of Rome was presented for the first time. Nine secondary metabolites were evidenced *i.e.*, pheophytin *a* (**1**), verbascoside (**2**), alyssonoside (**3**), apigenin (**4**), cirsimaritin (**5**), cirsiliol (**6**), 8-*O*-acetyl-harpagide (**7**), teucardoside (**8**) and quinic acid (**9**). Their presence is perfectly in accordance with previously published general results on the species, thus confirming the phytochemical knowledge on it.

Keywords: *Teucrium Capitatum* L. Subsp. *Capitatum*, Botanical Garden Of Rome, Phytochemical Analysis

Introduction

Teucrium capitatum L. subsp. *capitatum* (Fig. 1) is a suffruticose perennial plant belonging to the Lamiaceae family. It is morphologically characterized by an erected, slightly hairy stem which is woody at the base. The leaves are opposite, entire, and sessile. The inflorescence is branched, gathered in a cob with a white tomentose corolla formed by five small petals. The fruit is a schizocarp constituted by four light brown colored ovoidal mericarps (Pignatti, 1982).
After the recent modifications on its growth area, the species is now distributed from the Mediterranean Basin to Afghanistan (www.powo.science.kew.org). In Italy, it is present everywhere except in Lombardy, Trentino-Alto Adige and Valle d'Aosta, growing wild in garigues, dunes, arid and stony areas till the altitude of 1800 m a.s.l. (Conti et al., 2005).

Different phytochemical studies have been conducted on *T. capitatum* subsp. *capitatum* evidencing the presence of several classes of natural compounds like sesquiterpenoids, triterpenoids, diterpenoids, phenyl-ethanoid glycosides, flavonoids and iridoids (Sadeghi et al., 2022) but none has previously focused on an exemplar collected in the Botanical Garden of Rome. This represents the main reason why this work was begun because performing more phytochemical analyses on different populations of a same species is always necessary since it can provide more precise and complete information on its real phytochemical composition given that this is deeply affected by intrinsic and extrinsic factors (Liebelt et al., 2019). In this paper, a general phytochemical comparison with the previously published results on other populations of the species was also presented.

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Figure 1. Image of *Teucrium capitatum* L. subsp. *capitatum.*

Materials and methods

Plant material

The leaves of *T. capitatum* subsp. *capitatum* (4.5 g) were collected in the Botanical Garden of Rome located in Largo Cristina di Svezia, 23 A - 24, 00165 Roma RM (geographical coordinates: 41°53'32'' N, 12°27'57'' E) on July 13 in 2023. The botanical identification was performed by the botanist of the park and one of the authors (Dr Andrea Bonito) by comparing the morphological features with those available in the literature (Pignatti 1982). A sample of this collection is stored in our laboratory for further reference under the voucher code TCSC13072023.

Solvents and reagents

The following materials and solvents were used during this study: ethanol 96% for the extraction procedure; *n*-butanol, distilled water, methanol, *n*-hexane and ethyl acetate as pure solvents or in mixture among them as eluting systems for the column chromatography separation on silica gel (40–63 μm) used as stationary phase; 2N sulfuric acid for the developments of the TLCs; deuterated solvents ($CDCl_3$, CD_3OD and D_2O) for the identification of the secondary metabolites by means of NMR spectroscopy; HPLC-grade methanol for the identification of the secondary metabolites by means of mass spectrometry. All the solvents having RPE purity grade, if not differently specified, together with the deuterated solvents, the TLCs and HPLC-grade methanol were purchased from Merck (St. Louis, Missouri, USA) whereas silica gel was purchased from Fluka Analytical (Bergamo, Italy).

Instrumentation

NMR spectra were recorded at 298 K on a Jeol JNM-ECZ 600R spectrometer with a magnet operating at 14.09 T corresponding to a proton resonance frequency of 600.19 MHz and equipped with a Jeol multinuclear *z*-gradient inverse probehead. ^{1}H NMR spectra were acquired with 32 transients, a spectral width of 9013.7 Hz (corresponding to 15 ppm) and 64K data points for an acquisition time of 7.3 s. The recycle delay was set to 7.7 s to achieve complete resonance relaxation between successive scans. The chemical shifts were referenced to TMS (s, 0 ppm) for spectra in $CDCl_3$, the internal solvent signal of CD_2HOD (m5, 3.31 ppm) was the reference for spectra in CD_3OD while the HDO signal (s, 4.79 ppm) was set as reference for spectra in D_2O. MS spectra were acquired with a triple quadrupole mass spectrometer PE-Sciex API-3000® (Perkin Elmer Sciex, Toronto, ON, Canada), equipped with an ESI source operating in the negative and/or positive ion mode. The capillary ion voltage was set at 5000 V for the positive ionization and -4500 V for the negative one. High-purity nitrogen was used as a curtain gas (5 L/min) while air was employed as the nebulizer (2 L/min) and drying gas (30 psi). The temperature to heat the drying gas was set at 100 °C. The flow rate of sample infusion was 20 μL/min. MS spectra were acquired with 20 acquisitions per sample. The full width at half maximum (FWHM) was set at *m/z* 0.7 ± 0.1 in each mass-resolving quadrupole to operate with a unit resolution. The mass spectrometer operated in Full Scan mode in a mass spectral range of 100–1000 *m/z*. Data were acquired and elaborated by Analyst® 1.6 software (AB Sciex, Washington, USA).

Extraction, separation, and identification procedures

The leaves of *T. capitatum* subsp. *capitatum* (4.00 g) were extracted with ethanol 96% (about 300 mL) three times after a maceration of 96 h, each. The ethanol was evaporated at reduced pressure at 50 °C until a water suspension was obtained. Throughout the concentration procedure, pH of the extracting solution was checked on litmus paper to verify that it was not too acid or basic (meaning between the range 5.5–8.5) because an extreme acidity or alkalinity might cause unwanted secondary reactions in the extract such as the hydrolysis of ester and glycosidic bonds. In this case, pH was about 8. The obtained dried dark green extract weighed 1 g. The whole of this was subjected to a first chromatographic separation on silica gel (40 g, ratio about 1:40 *w/w*). The eluting system consisted of a mixture of *n*-butanol and distilled water at the concentration ratio of 82:18 *v/v* (400 mL). During the chromatographic run, the polarity of the eluting system was raised to let the elution of

more polar compounds by passing to a mixture of *n*-butanol, methanol, and distilled water at the concentration ratio of 70:10:30 *v/v/v* (300 mL). From this first chromatographic separation, six compounds were identified by comparison with spectroscopic and spectrometric data reported in the literature: pheophytin *a* (**1**) (Frezza et al., 2019a) in mixture with lipids (ratio 1:15 *w/w*) from the combined fractions 7-22 (70.0 mg); verbascoside (**2**) (Frezza et al., 2019b) in mixture with alyssonoside (**3**) (Çalis et al., 1992) (ratio 6:1 *w/w*) from the combined fractions 39-42 for the total weight of 5.7 mg; 8-*O*-acetyl-harpagide (**7**) (Venditti et al., 2016a**)** in mixture with alyssonoside (**3**) (Çalis et al., 1992) in ratio 1:10 *w/w* from the combined fractions 65-78 (7.7 mg); teucardoside (**8**) (Frezza et al., 2023) in mixture with 8-*O*-acetyl-harpagide (**7**) (Venditti et al., 2016a**)** and saccharides (ratio not calculable) from the combined fractions 79-91 (25.2 mg); quinic acid (**9**) (Frezza et al., 2019a) as almost pure compound from the methanol column wash for the weight of 71.1 mg. Since not all the secondary metabolites could be perfectly identified from this first chromatographic procedure, a second chromatographic step was performed on the assembly of fractions 7-38 for the total weight of 251.4 mg using 10 g of silica gel as stationary phase (ratio about 1:40 *w/w*). The initial eluting system consisted of a mixture of *n*-hexane and ethyl acetate in ratio 95:5 *v/v* (50 mL) but during the chromatographic run, the polarity of this eluting mixture was raised passing to concentration ratios of 9:1 *v/v* (100 mL), 8:2 *v/v* (100 mL), 7:3 *v/v* (100 mL), 6:4 *v/v* (100 mL), 1:1 *v/v* (100 mL), 4:6 *v/v* (100 mL), 2:8 *v/v* (100 mL) in order to let the elution of more polar compounds. From this chromatographic step, three further compounds were identified: apigenin (**4**) and cirsimaritin (**5**) (Frezza et al., 2023) in mixture in ratio 1:6 *w/w* from the combined fractions 122-124 (10 mg); apigenin (**4**), cirsimaritin (**5**) and cirsiliol (**6**) (Frezza et al., 2023) in mixture (ratio not calculable) from the combined fractions 142-166 (6.3 mg).

NMR and MS data of the identified metabolites

Pheophytin *a* (**1**): ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.50 (1H, s, H-10), 9.37 (1H, s, H-5), 8.53 (1H, s, H-20), 7.97 (1H, dd, *J* = 18.2/11.7 Hz, H-3'), 6.17 (1H, d, *J* = 12.2 Hz, H_b-3''), 5.15-5.10 (1H, overlapped, H-22), 3.87 (3H, s, H-13^{IV}), 3.67 (3H, s, H-12'), 3.38 (3H, s, H-2'), 3.22 (3H, s, H-7'), 1.87 (3H, s, H-18'), 1.71-1.64 (6H, overlapped signals, Me-8', Me-23), 0.80-0.75 (12H, overlapped signals, H-24, H-25, H-26, H-27).
ESI-MS: *m/z* 893.31 $[M+Na]^+$.
Verbascoside (**2**): ^{1}H NMR (600 MHz, CD_3OD) δ: 7.60 (1H, d, *J* = 15.9 Hz, H-β), 7.06 (1H, d, *J* = 2.0 Hz, H-2'), 6.96 (1H, dd, *J* = 8.1/2.0 Hz, H-6'), 6.78 (1H, d, *J* = 8.1 Hz, H-5'), 6.69 (1H, d, *J* = 2.3 Hz, H-2''), 6.68 (1H, d, *J* = 8.1 Hz, H-5''), 6.57 (1H, dd, *J* = 8.1/2.3 Hz, H-6''), 6.28 (1H, d, *J* = 15.9 Hz, H-α), 5.18 (1H, d, *J* = 1.7 Hz, H-1'''), 4.38 (1H, d, *J* = 7.9 Hz, H-1), 4.00-3.35 (overlapped signals of saccharides), 2.83-2.78 (1H, overlapped, H-β'), 1.08 (3H, d, *J* = 6.2 Hz, Me- Rha).
ESI-MS: *m/z* 623.34 $[M-H]^-$.
Alyssonoside (**3**): ^{1}H NMR (600 MHz, CD_3OD) δ: 7.59 (1H, d, *J* = 15.8 Hz, H-β), 7.19 (1H, d, *J* = 2.0 Hz, H-2'), 7.11 (1H, dd, *J* = 8.2/2.0 Hz, H-6'), 6.75 (1H, d, *J* = 8.2 Hz, H-5'), 6.67 (1H, d, *J* = 2.1 Hz, H-2''), 6.65 (1H, d, *J* = 8.1 Hz, H-5''), 6.59 (1H, dd, *J* = 8.1/2.1 Hz, H-6''), 6.29 (1H, d, *J* = 15.8 Hz, H-α), 5.16 (1H, d, *J* = 1.7 Hz, H-1'''), 4.92 (1H, d, *J* = 2.0 Hz, H-1^{IV}), 4.35 (1H, d, *J* = 7.8 Hz, H-1), 4.00-3.35 (overlapped signals of saccharides), 3.88 (3H, s, 3'-OMe), 2.83-2.78 (1H, overlapped, H-β'), 1.06 (3H, d, *J* = 6.2 Hz, Me- Rha).
ESI-MS: *m/z* 793.78 $[M+Na]^+$; *m/z* 769.71 $[M-H]^-$.
Apigenin (**4**): ^{1}H NMR (600 MHz, CD_3OD) δ: 7.86 (1H, d, *J* = 8.9 Hz, H-2' and H-6'), 6.95 (1H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.61 (1H, s, H-3), 6.47 (1H, d, *J* = 2.1 Hz, H-8), 6.22 (1H, d, *J* = 2.2 Hz, H-6).
ESI-MS: *m/z* 293.21 $[M+Na]^+$; *m/z* 269.16 $[M-H]^-$.
Cirsimaritin (**5**): ^{1}H NMR (600 MHz, CD_3OD) δ: 7.91 (1H, d, *J* = 8.9 Hz, H-2' and H-6'), 6.95 (1H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.84 (1H, s, H-8), 6.68 (1H, s, H-3), 3.99 (3H, s, 7-OMe), 3.84 (3H, s, 6-OMe).
ESI-MS: *m/z* 337.30 $[M+Na]^+$.
Cirsiliol (**6**): ^{1}H NMR (600 MHz, CD_3OD) δ: 7.44 (1H, d, *J* = 8.3/2.3 Hz, H-6'), 7.41 (1H, d, *J* = 2.3 Hz, H-2'), 6.92 (1H, d, *J* = 8.3 Hz, H-5'), 6.81 (1H, s, H-8), 6.61 (1H, s, H-3), 3.99 (3H, s, 7-OMe), 3.84 (3H, s, 6-OMe).
ESI-MS: *m/z* 353.31 $[M+Na]^+$.
8-*O*-acetyl-harpagide (**7**): ^{1}H NMR (600 MHz, CD_3OD) δ: 6.39 (1H, d, *J* = 6.4 Hz, H-3), 6.07 (1H, d, *J* = 1.0 Hz, H-1), 5.00 (1H, overlapped with solvent signal, H-4), 4.60 (1H, d, *J* = 7.9 Hz, H-1'), 3.95-3.38 (overlapped signals of saccharide), 2.86 (1H, br. s, H-9), 2.21-2.12 (1H, m, H-7a), 2.09-2.03 (1H, m, H-7b), 2.02 (3H, s, OAc), 1.45 (3H, s, H-10).
ESI-MS: *m/z* 429.58 $[M+Na]^+$; *m/z* 405.47 $[M-H]^-$.
Teucardoside (**8**): ^{1}H NMR (600 MHz, D_2O) δ: 6.50 (1H, d, *J* = 6.3 Hz, H-3), 6.14 (1H, br. s, H-7), 6.01 (1H, d, *J* = 1.3 Hz, H-1), 5.35 (1H, d, *J* = 1.7 Hz, H-1''), 5.06 (1H, dd, *J* = 6.3/0.7 Hz, H-4), 4.69 (1H, overlapped with solvent signal, H-1'), 4.02-3.44 (overlapped signals of saccharides), 2.34 (3H, s, H-10), 1.24 (3H, d, *J* = 6.3 Hz, Me-Rha).
ESI-MS: 513.61 *m/z* $[M+Na]^+$.
Quinic acid (**9**): ^{1}H NMR (600 MHz, D_2O) δ: 4.15-4.07 (1H, m, H-4), 3.80-3.72 (1H, m, H-5), 3.64-3.54 (1H, m, H-3), 2.26-2.15 (4H, m, H_a-2, H_b-2, H_a-6, Hb-6).
ESI-MS: 214.58 *m/z* $[M+Na]^+$; *m/z* 191.31 $[M-H]^-$.

Results

The phytochemical analysis on the leaves of *T. capitatum* subsp. *capitatum* collected in the Botanical Garden of Rome led to the identification of nine compounds: pheophytin *a* (**1**), verbascoside (**2**), alyssonoside (**3**), apigenin (**4**), cirsimaritin (**5**), cirsiliol (**6**), 8-*O*-acetyl-harpagide (**7**), teucardoside (**8**) and quinic acid (**9**) (Fig. 2).

These compounds belong to five different classes of natural compounds *i.e.*, degradation products of chlorophylls (**1**), phenyl-ethanoid glycosides (**2-3**), flavonoids (**4-6**), iridoids (**7-8**) and organic acids (**9**).

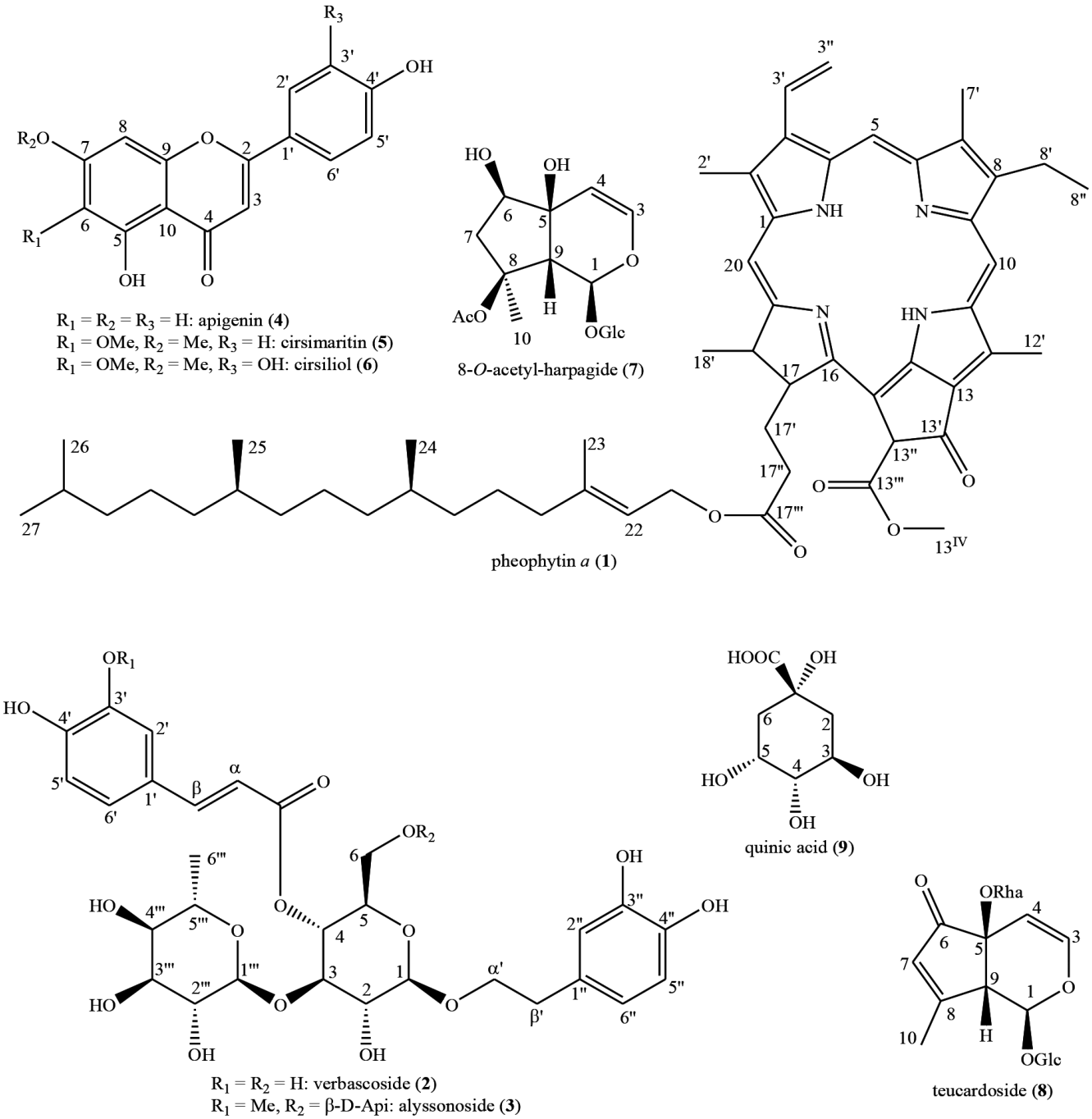

Figure 2. Structures of the identified compounds in *T. capitatum* subsp. *capitatum*.

Discussion

Except for pheophytin *a* (**1**) which derives from chlorophyll *a* and is probably an artifact of extraction (Venditti et al., 2020), verbascoside (**2**), alyssonoside (**3**), apigenin (**4**), cirsimaritin (**5**), cirsiliol (**6**), 8-*O*-acetyl-harpagide (**7**), teucardoside (**8**) and quinic acid (**9**) have been already evidenced in several populations of the species collected in many areas of the world (De Marino et al., 2012; Goulas et al., 2012; Mitreski et al., 2014; Venditti et al., 2017a, 2017b; Mihailović et al., 2020; Abdullah et al., 2022; Toplan et al., 2022), thus confirming their wide occurrence in this *taxon*. In particular, the presence of 8-*O*-acetyl-harpagide (**7**) and teucardoside (**8**), alone and along with verbascoside (**2**) and alyssonoside (**3**), is extremely important since they all confirm the botanical classification of the studied sample as a member of the *Teucrium* genus, of the Lamiaceae family and of the Asterids given that they represent their typical phytochemical compounds (Frezza et al., 2019c; Jensen et al., 1992). The absence of *neo*-clerodane diterpenes having a furan ring, typical phytochemical compounds of *Ajugoideae* sub-family (Frezza et al., 2019a) where this species is included, is also noteworthy and it is different from previous results (Abdullah et al., 2022; Bedir et al., 1999; Bruno et al., 2003; Sadaka et al., 2017). Yet, this peculiarity has been already observed in different *Ajugoideae* species collected in the continental Italy (Venditti et al., 2016a, 2016b; Frezza et al., 2017, 2018, 2019d, 2023) unlike the Islands (Fernández et al., 1985; Bruno et al., 2002). The reason behind this is currently under investigation even if preliminary considerations lead to hypothesize that the environment may indeed be responsible since the same methodology has always been adopted and in the species collected in Iran, these compounds have been found (Venditti et al., 2017a, 2017b). This aspect surely needs further studies and in-depth analyses.

Conclusions

The phytochemical analysis on the leaves of *T. capitatum* subsp. *capitatum* collected in the Botanical Garden of Rome led to the identification of nine compounds, four of which, also in combination, are typical phytochemical compounds of the species, family, clade. Their occurrence in this *taxon* has already been evidenced, thus confirming the previous phytochemical results. On the other hand, the absence of *neo*-clerodane diterpenes having a furan ring is an important difference from the previous studies even if this has been already recorded in Italian *Ajugoideae* populations, maybe due to the environment.

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