Secondary metabolites from *Teucrium polium* L. collected in Southern Iran

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In this paper a comprehensive phytochemical analysis of the ethanolic extract obtained from a sample of *Teucrum polium* collected in Southern Iran is reported. Several phenolic components were identified such as flavonoids and phenylethanoid glycosides which together resulted to be the principal components of the extract. In particular, these compounds were **cirsilineol** (**1**), **apigenin 7-*O*-rutinoside** (**isorhoifolin**) (**2**), **cirsimaritin** (**4**), **diosmetin** (**5**), **apigenin** (**6**), **cirsiliol** (**7**) and, lastly, **poliumoside** (**3**). Their presence may justify, from the phytochemical point of view, the ancient ethno-medicinal uses of this species as antispasmodic, anti-inflammatory, anti-diabetic, hypolipidemic and **antirheumatic**. Besides these health-promoting compounds, it was yet evidenced a minor presence of *neo*-clerodane diterpenoids which are, actually, known to possess hepatotoxic properties. In detail, these compounds were **10-β-hydroxy-teucjaponin B** (**8**), **picropolin** (**9**) and **teupolin I** (**10**). Indeed, their presence underlines the necessity of a more accurate screening for this class of compounds on the raw materials devoted to botanicals and ethno-medicinal uses. Iridoids, considered to be marker compounds for the genus and for the Lamiaceae family, were completely absent in the studied sample, instead. This fact reveals the presence of an intraspecific variability for these metabolites in the studied species.

Keywords: *Teucrum polium* L.; Flavonoids; Phenylpropanoid glycosides; Neo-clerodanes; Chemotaxonomy; Ethno-medicine

Introduction:

Felty germander, *Teucrium polium* L., is a perennial herbaceous plant with a woody base and a round stalk as well as a pubescent nature, which is comprised in the Lamiaceae family (subfamily Ajugoideae). It is a perennial chamaephytic subshrub owning an erect stem, 10 - 12 cm tall, fully branched in the upper part. The flowers are colored from pink to yellow and are gathered in small and

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dense verticillasters. They bloom from April to August. The leaves, oblong or linear (2 cm long and up to 4 mm wide) are sessile and possess an intact and folded margin in the lower part which becomes crenate and outstretched in the upper one (Negri 1979).

Its scientific name derives from the union of two greek terms, “τεύκριον – teúcrion”, an ancient Trojan king who was the first one to utilize this plant for medical purposes, according to the Roman historiographer Pliny the Young, and "πολιόν - poliòn" meaning grey-whitish, referring to the colour of the flowers.

This species is spread in almost all Mediterranean countries with extensions of its areal in Southwestern Asia (Feinbrun-Dothan 1978) and Europe. Its typical habitat is represented by dry and stony hills till the altitude of 3000 m a.s.l. (Kovacevic et al. 2001). In Italy, it is present almost everywhere along the territory (Pignatti 1982; Conti et al 2005) while in Iran it grows mainly on the hills and the deserts of the Mediterranean and Western Irano-Turanian geographical region where is locally called "Kalpooreh" (Gorgini Shabankare et al 2015).

The species shows a very ancient popular tradition for medical purposes and has been utilized in Mediterranean countries for many therapeutic activities i.e. antispasmodic and hypoglycemic (Abu-Irmaileh and Afifi 2003), anti-inflammatory, anti-diabetic and anti-rheumatic (Tariq et al. 1989; Abdollahi et al. 2003), hypolipidemic, antinociceptive and antioxidant (Esmaeili and Yazdanparast, 2004). Moreover, other studies suggest it can also be useful to fight bacteria, spasms and anorexia (Autore et al., 1984).

Several phytochemical studies have been already conducted on this species reporting many different components: tannins (Rudakova et al. 2014); saponin (Elmasri et al. 2015); diterpenoids (Piozzi et al. 2005) among which teucrin is one of the most important; flavonoids especially apigenin derivatives (Pacifico et al. 2012; D’Abrosca et al. 2013); iridoids with 8-*O*-acetyl-harpagide (Rizk et al. 1986) and teucardoside (Essam 1998) as marker compounds. Even the essential oil composition has been investigated (Gorgini Shabankare et al. 2015; Kerbouche et al., 2015; Sadeghi et al. 2014; Moghtader 2009) and revealed the presence of different chemotypes showing a composition influenced by the geographic origin of the samples.

In continuation of our study on Lamiaceae species and in particular on *T. polium* from Iran (Venditti et al., 2017), this paper reports the phytochemical analysis of the ethanolic extract obtained from asample collected in Southern Iran.

Materials and methods:

Solvents and reagents.

During the study the following solvents and reagents were used: ethanol 96% for the extraction procedure; *n*-butanol, distilled water, chloroform, methanol, ethyl-acetate and *n*-hexane as pure compounds or in mixtures among them all, for the separation procedure by chromatography column on silica gel (particle sizes 40-63 μm); H_2SO_4 2N, $FeCl_3$ 3% (w/v) solution and a vanillin/HCl 3% (w/v) methanolic solution as spray reagents for TLCs; $CDCl_3$ and CD_3OD, as deuterated solvent for the sample preparation for NMR spectroscopy analysis; methanol having RS purity grades to dissolve samples into before analysis in MS spectrometry.

Instruments.

The following instruments were used during the present study: Rotavapor RII by Büchi coupled with a "Jet Standard" vacuum pump by "General Scientific Instrument" for the solvent evaporation at reduced pressure; lyophilizer by "Analitica De Mori" company.

A Varian (now Agilent Technologies) Mercury 300 MHz instrument and/or a Bruker Avance II 400 MHz instrument were utilized to perform NMR spectra. Chemical shifts were expressed in ppm from TMS for spectra in $CDCl_3$ while the internal solvent signal (m5) at 3.31 ppm was used as reference for spectra in deuteromethanol.

MS spectra were, instead, performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source that operated in the negative and/or positive ion mode. The flow rate of the sample infusion was 10 μL/min. With 100 acquisitions per spectrum. Data were analysed by using the MassLynx software developed by Waters.

Plant Material and Extraction

The plant material was collected in the territory of the Kerman province located in South Western Iran and, in particular, on the Koohpayeh mountains (geographic coordinates: 30°31'57" N, 57°11'42" E), from a wild population of flowering plants, at an altitude of about 2200 m a.s.l., in late June 2014.

The botanical identification was performed by one of us (Dr. Seyed Majid Majd Zadeh) using available literature (Mozaffarian 1996).

A sample of the studied accession is stored in our laboratory under the voucher number TP0515IS for further references.

A portion of 149.5 g of plant materials was exhaustively extracted with ethanol 96% (1.8 L x 3 extractions, 48 h of maceration). The filtered ethanolic solutions were gathered and concentrated altogether at reduced pressure until a water suspension was obtained. The dried extract was obtained through freeze-drying procedure to preserve possible temperature-sensitive components, obtaining 18.2 g of crude dry material.

Isolation and identification of the components.

The chromatographic separation was conducted on an aliquot of 3.0 g of the crude dry extract on silica gel (90.0 g) CC using *n*-BuOH/H_2O (82:18 v/v) as mobile phase. During the chromatographic run the polarity was increased passing to an *n*-BuOH/MeOH/H_2O solution at concentration 70:10:30 (v/v/v) in order to favor the elution of the more polar components. From this step 79 fractions with different mixtures of components were obtained. Fractions [5-20A] (498.7 mg) were furtherly separated on silica gel CC (25.0 g) and eluted with a mixture of chloroform/methanol. The initial concentration of the solution was 97:3 (v/v) (200 ml) but this was gradually increased by rising the polarity to 9:1 (v/v) (100 ml), 8:2 (v/v) (120 ml), 7:3 (v/v) (300 ml) and, lastly, to 6:4 (v/v) (300 ml).

From this step six compounds were identified: **cirsilineol** (**1**) [Fr.13B] (6.0 mg) (Alwahsh et al 2015) in mixture (~1:1:1:1) with **10-β-hydroxy-teucjaponin B** (**8**) (Coll and Tandrón 2005), **picropolin** (**9**) (Brieskorn and Pfeuffer 1967; Malakov et al. 1979; Fernandez et al. 1986) and **teupolin I** (**10**) (Malakov et al. 1979); **apigenin-7-*O*-rutinoside** (**isorhoifolin**) (**2**) [Fr.103-108B] (19.4 mg) (Kokotkiewicz et al. 2012; Boghrati et al. 2016); **poliumoside** (**3**) [Fr.119-144B] (45.8 mg) (Andary et al, 1985).

A third separation step was conducted on the assembly of fractions [Fr.14-46B] deriving from the second step for a total weight of 325.9 mg. 10.0 g of acidic silica gel and a mixture of *n*-hexane/ethyl acetate (85:15 v/v) previously saturated with CO_2 was used. The polarity of this solution was gradually increased during the run and changed to 70:30, 60:40 and, lastly, 50:50 (v/v). 215 fractions were collected.

From this step four compounds were identified: **cirsimaritin** (**4**) (Alwahsh et al. 2015) [Fr.46-56C] (7.4 mg) in mixture (10:2:1) with **4'-*O*-methyl luteolin** (**diosmetin**) (**5**) (Park et al. 2007) and **apigenin** (**6**) (Chaturvedula and Prakash 2013); **cirsimaritin** (**4**) (Alwahsh et al. 2015) [Fr.57-86C] (17.5 mg); **cirsimaritin** (**4**) and **cirsiliol** (**7**) (Alwahsh et al. 2015) in mixture (2:1) [Fr.87-90] (1.9 mg); **cirsiliol** (**7**) (Alwahsh et al. 2015) [Fr.96-108C] (5.3 mg).

NMR and Mass spectra data of all the isolated compounds.

Cirsilineol (**1**): ^1H NMR (300 MHz, $CDCl_3$) δ: 7.41 (1H, d, *J* = 2.0 Hz, H-2'), 7.34 (1H, br d, *J* = 8.6 Hz, H-6'), 7.03 (1H, d, *J* = 8.4 Hz, H-5'), 6.58 (1H, s, H-8), 6.55 (1H, s, H-3), 4.00 (3H, s, 3'-OMe), 3.97 (3H, s, 7-OMe), 3.92 (3H, s, 6-OMe).

ESI-MS: *m/z* 344.93 $[M+H]^+$.

Apigenin-7-*O*-rutinoside (**isorhoifolin**) (**2**): ^1H NMR (300 MHz, CD_3OD) δ: 7.87 (2H, d, *J* = 8.8 Hz, H-2', H-6'), 6.94 (2H, d, *J* = 8.8 Hz, H-3', H-5'), 6.75 (1H, d, *J* = 2.0 Hz, H-8), 6.64 (1H s, H-3), 6.51 (1H, d, *J* = 2.0 Hz, H-6), 5.04 (1H, d, *J* = 7.0 Hz, H-1''), 4.72 (1H, br s,H-1'''), 1.17 (3H, d, *J* = 6.2 Hz, H-6''').

^{13}C NMR (75 MHz, CD_3OD) δ 184.0 (C-4), 166.8 (C-7), 164.7 (C-2), 163.0 (C-4'), 162.8 (C-9), 158.9 (C-5), 129.6 (C-2', C-6'), 123.1 (C-1'), 117.1 (C-3', C-5'), 107.1 (C-10), 104.1 (C-3), 102.1 (C-1'''),

101.5 (C-1''), 101.1 (C-8), 96.2 (C-6), 77.8 (C-3''), 77.1 (C-5''), 74.7 (C-2''), 74.1 (C-4'''), 72.4 (C-3'''), 72.1 (C-2'''), 71.3 (C-4''), 69.9 (C-5'''), 67.4 (C-6''), 17.9 (C-6''').

ESI-MS: *m/z* 600.87 $[M+Na]^+$; *m/z* 577.09 $[M-H]^-$.

Poliumoside (**3**): ^{1}H NMR (300 MHz, CD_3OD) δ: 7.60 (1H, d, *J* = 15.9 Hz, H-β''), 7.07 (1H, br s, H-2''), 6.96 (1H dd, *J* = 8.2, 1.9 Hz, H-6''), 6.78 (1H, d, *J* = 8.2 Hz, H-5''), 6.70 (1H, d, *J* = 2.1 Hz, H-2'), 6.69 (1H, d, J = 8.0 Hz, H-5'), 6.57 (1H, dd, *J* = 8.0, 2.1 Hz, H-6'), 6.28 (1H, d, *J* = 15.9 Hz, H-α''), 5.19 (1H, br s, H-1^{IV}), 4.63 (1H, br s, H-1'''), 4.38 (1H, d, *J* = 7.9 Hz, H-1(Glc)), 4.03 - 3.26 (overlapped carbohydrate signals), 2.80 (2H, br t, *J* = 7.1 Hz, H-β'), 1.20 (3H, d, *J* = 6.2 Hz, H-6^{IV}), 1.08 (3H, d, *J* = 6.1 Hz, H-6''').

^{13}C NMR (75 MHz, CD_3OD) δ: 168.0 (COO caff), 149.8 (C-4''), 148.0 (C-β''), 146.8 (C-3''), 146.1 (C-3'), 144.7 (C-4'), 131.4 (C-1'), 127.6 (C-1''), 123.2 (C-6''), 121.3 (C-6'), 117.1 (C-2'), 116.5 (C-5''), 116.4 (C-5'), 115.2 (C-2''), 114.7 (C-α''), 104.3 (C-1(Glc)), 103.0 (C-1^{IV}), 102.2 (C-1'''), 81.6 (C-3(Glc)), 76.1 (C-2(Glc)), 74.7 (C-5(Glc)), 73.9 (C-4'''), 73.7 (C-4^{IV}), 72.4 (C-2'''), 72.3 (C-α'), 72.2 (C-2^{IV}), 72.1 (C-3'''), 72.0 (C-3^{IV}), 70.4 (C-5'''), 70.3 (C-4(Glc))69.9 (C-5^{IV}), 67.5 (C-6(Glc)), 30.8 (C-β'),18.4 (C-6'''), 18.0 (C-6^{IV}).

ESI-MS: *m/z* 792.97 $[M+Na]^+$; *m/z* 768.85 $[M-H]^-$.

Cirsimaritin (**4**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (2H, d, *J* = 8.9 Hz, H-2', H-6'), 6.97 (2H, d, *J* = 8.9 Hz, H-3', H-5'), 6.59 (1H, s, H-8), 6.55 (1H, s, H-3), 3.97 (3H, s, 7-OMe), 3.93 (3H, s, 6-OMe).

ESI-MS: *m/z* 337.19 $[M+Na]^+$; *m/z* 651.40 $[2M+Na]^+$.

4'-*O*-methyl luteolin (**diosmetin**) (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (1H, dd, *J* = 8.5, 1.8 Hz, H-6'), 7.57 (1H, d, *J* = 1.8 Hz, H-2'), 6.99 (1H, d, *J* = 8.5 Hz, H-5'), 6.56 (1H, s, H-3), 6.45 (1H, d, *J* = 2.1 Hz, H-8), 6.29 (1H, d, *J* = 2.1 Hz, H-6), 3.96 (3H, s, 4'-OMe).

ESI-MS: *m/z* 301.34 $[M+H]^+$.

Apigenin (**6**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 9.0 Hz, H-2', H-6'), 6.96 (2H, d, *J* = 9.0 Hz, H-3', H-5'), 6.60 (1H, s, H-3), 6.36 (1H, br s, H-8), 6.21 (1H, br s, H-6).

ESI-MS: *m/z* 271.42 $[M+H]^+$.

Cirsiliol (**7**): ^{1}H NMR (400 MHz, CD_3OD) δ: 7.44 (1H, dd, *J* = 8.3, 2.2 Hz, H-6'), 7.41 (1H, d, *J* = 2.2 Hz, H-2'), 6.92 (1H, d, *J* = 8.3 Hz, H-5'), 6.80 (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* 331.18 $[M+H]^+$.

10-β-hydroxy-teucjaponin B (**8**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (1H, br s, H-16), 7.45 (1H, br s, H-15), 6.39 (1H, br s, H-14), 5.11 (1H, m, H-19a), 4.70 (1H, m, H-19b), 4.16 (1H, br d, J = 11.0 Hz,, H-6), 2.12 (3H, s, AcO), 0.99 (3H, d, *J* = 7.0 Hz, H-17).

ESI-MS: *m/z* 442.93 $[M+Na]^+$.

Picropolin (**9**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (1H, br s, H-16), 7.42 (1H, br s, H-15), 6.38 (1H, br s, H-14), 5.52 (1H, m, H-12), 4.99 (1H, br d, *J* = 12.8 Hz, H-19a), 4.79 – 4.64 (1H, m, H-19b), 3.23 (1H, overlapped with other signals, H-18a), 2.55 (1H, d, *J* = 3.5 Hz, partially overlapped, H-18b), 2.16 (3H, s, AcO), 0.85 (3H, d, *J* = 7.1 Hz, H-17).
ESI-MS: *m/z* 440.93 $[M+Na]^+$.

Teupolin I (**10**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (1H, d, *J* = 3.4 Hz, H-16), 7.40 (1H, br s, H-15), 6.35 (1H, br s, H-14), 5.31 – 5.22 (1H, m, H-12), 4.99 (1H, d, *J* = 12.4 Hz, H-19a), 4.57 (1H, d, *J* = 12.4 Hz, H-19b), 3.62 – 3.47 (1H, m, H-6), 3.23 – 3.13 (1H, m, H-18a), 2.06 (3H, s, AcO), 0.96 (3H, d, *J* = 6.5 Hz, 1H).
ESI-MS: *m/z* 426.94 $[M+Na]^+$.

Results and discussion:

Results

The phytochemical analysis of *T. polium* from Southern Iran revealed the presence of several phenolic components (Figure 1) mainly represented by mono-, di- and tri-metoxylated flavonoids aglycones. In detail these were **cirsilineo**l (**1**), **cirsimaritin** (**4**), **diosmetin** (**5**) and **cirsiliol** (**7**). Yet, **apigenin** (**6**) and its **7-*O*-rutinoside derivative** (**isorhoifolin**) (**2**) were evidenced, too.
In addition to them, **poliumoside** (**3**), a phenylethanoid glycoside (PhGs) with chemo-taxonomic relevance in Lamiaceae family and three *neo*-clerodane diterpenoids namely **10-β-hydroxy-teucjaponin B** (**8**), **picropolin** (**9**) and **teupolin I** (**10**) weres also recognized.

Discussion

Flavonoids (**1**) and (**4-7**) have already been identified in the nominal species (Harborne et al. 1986; Verykokidou-Vitsaropoulou and Vajias 1986; Kawashty et al. 1999; Esmaeili and Sadeghi 2009; Galstyan 2014) but also in *T. polium* spp. *capitatum* (L.) Arcang. (syn. of *T. capitatum* L.) (Stefkov et al 2011), in *T. polium* var. *pilosum* Decne. (syn. of *T. decaisnei* C.Presl) and in *T. polium* var. *alba* (= *T. polium* subsp. *album* (Poir.) Breistr. (syn. of *T. capitatum* L.) (Rizk et al. 1986).
Moreover, they have also been reported in other species of the genus such as *T. barbeyanum* Asch. & Taub. ex E.J.Durand & Barratte (Alwahsh et al. 2015), *T. leucocladum* Boiss. (Kawashty et al. 1999), *T. alyssifolium* Stapf (Topcu et al. 1996), *T. pilosum* (Decne.) Asch. & Schweinf. (syn. of *T. decaisnei* C. Presl) (Hawas et al. 2008), *T. orientale* L. var. *orientale* (syn. of *T. orientale* L.) (Çakir et al. 2006), *T. chamaedrys* L. and *T. montanum* L. (Panovska et al. 2005). Thus, the methylated flavonoid aglycones resulted to be quite widespread in this genus (Table 1) as well as **apigenin** (**6**). It is worth to note that luteolin, not recognized from the studied sample, resulted instead the main flavonoid constituent in samples of Macedonian origin in all of the phenological development (Stefkov et al,

2009). In *T. polium* from Southern Iran the main aglycone flavonoid resulted to be **cirsimaritin** (**4**) and, in general the presence of methylated derivatives (**1**, **5**, **7**) resulted to be more abundant in respect to the not methylated constituents (**6**).

On the contrary, **apigenin-7-*O*-rutinoside** (**isorhoifolin**) (**2**) has been previously reported only from a few species of the section Polium , as *T. polium* var. *gnaphalodes* Benth. (syn. of *T. capitatum* L.) (Boghrati et al. 2016), *T. freynii* E.Rev. ex Willk., *T. cossonii* D.Wood, *T. carthaginense* Lange, *T. pii-fontii* (P.Palau) Greuter & Burdet (syn. of *T. capitatum* subsp. *majoricum* (Rouy) Nyman) (Harborne et al. 1986) and in the nominal species (Galstyan 2014). It resulted to be a more widespread constituent in species comprised in the section Chamaedrys (Harborne et al. 1986).

All the isolated flavonoids are responsible for numerous biological activities and, in particular, the antioxidant one has been widely studied (Panovska et al. 2005; Çakir et al. 2006; Pacifico et al. 2012; D'Abrosca et al. 2013; Alwahsh et al. 2015). Yet, their implication in the antibacterial activity has been also demonstrated (Al-Kufaishi and Al-Mashhedy 2012; Elmasri et al. 2015; Dridi et al, 2016), as protective compounds on pancreatic B cells (Esmaeili and Sadeghi 2009) and as insulinotropic and antihyperglycemic molecules (Stefkov et al. 2011) also when compared with metformin and glibenclamide (two synthetic antidiabetic drugs) in *in vivo* experiments in both normoglycemic (Ireng et al, 2016) and streptozotocin-induced diabetic rats (Sarkarizi et al, 2015), resulting so very useful in the treatment of diabetes.

Poliumoside (**3**) resulted to be the only phenylethanoid glycoside recognized in the studied accession. PhGs have chemo-taxonomic relevance for the Lamiaceae family (Jensen 1992) and, in particular, for the section Polium within the studied genus (Andary et al. 1988).

Its presence is perfectly in accordance with the current botanical classification of *T. polium* representing a constituent of the nominal species (Oganesyan et al. 1992; De Marino et al. 2012; Galstyan 2014) as well as of its variety, *T. polium* var. *gnaphalodes* Benth. (syn. of *T. capitatum* L.) (Boghrati et al. 2016) or near species such as *T. belion* (Andary et al. 1985). Until now, it resulted absent only in *T. mideltense* (Batt.) Humbert, an endemic species from Morocco (El Oualldi et al. 1996).

Compound (**3**) is also endowed with interesting biological activities which range from the antioxidant one (De Marino et al. 2012; Goulas et al. 2012) to the anti-tyrosinase (Boghrati et al. 2016), neuroprotective (Koo et al. 2005), antibacterial (Oganesyan et al. 1992) and DNA polymerases - inhibitory actions (Iida et al. 2003).

Both flavonoids (**1**, **2** and **4-7**) and **poliumoside** (**3**) may be responsible for the therapeutic properties attributed to this species, and provide a rationale for its ancient traditional uses in ethno-medicine, from the phytochemical point of view. The biological activities may be related to their polyphenolic nature. In fact the structure of flavonoids is compatible with the roles of both substrates and inhibitors of tyrosinase due to the presence of several hydroxyl substituents in both the A and B rings of the

flavane skeleton. Tyrosinase is a copper-containing oxidase which catalyzes the first two steps of melanine synthesis starting from tyrosine oxidation to dopaquinone and compounds which may coordinate the copper are strong inhibitor of tyrosinase. The *meta*- and *orto*- dihydroxyl substitution present in flavonoids (but also in tyrosol and caffeoyl derivatives such as phenylpropanoids) may be effective in complexing the copper of the active site of tyrosinase thus inactivating the enzyme (Kubo et al, 2000; Kim et al, 2006 Zhang et al, 2007). Another two structural motif resulted crucial in the tyrosinase inhibition: the presence of a *p*-coumaroyl moiety (Kubo et al, 2004), which is present in the phenylpropanoid derivative **poliumoside** (**3**), together with a *orto*-diphenol substitution (present in both the caffeoyl and tyrosyl portions of (**3**) and also in the B ring of some of the identified flavonoids). The latter functionalization (*orto*-diphenol, catechol) may led to a irreversible enzyme inhibition (Haghbeen et al, 2004) with a mechanism extensively studied (Waley, 1985).

The antidiabetic action of polyphenols may be due to several mechanisms: inhibition of α-amylase and α-glucosidase, inhibition of glucose absorption, stimulation of insulin secretion and balance the glucose release from the liver/glucose uptake by the tissues (Hanhineva et al, 2010; Sirichai, 2017). The polyphenols identified in *T. polium* may interact with the glucose metabolism at several levels. In fact, both flavonoids and phenylpropanoids resulted effective as α-glucosidase inhibitors (Yin et al, 2014), may modulate the glucose homeostasis by interact with its absorption (Manzano and Williamson, 2010), modulate the insulin release (Hii and Howell, 1985) or increase the glucose uptake in adipocytes (Prabhakar and Doble, 2011).

The minor components of the ethanolic extract obtained from *T. polium* collected in Southern Iran resulted to be three *neo*-clerodane diterpenoids namely **10-β-hydroxy-teucjaponin B** (**8**), **picropolin** (**9**) and **teupolin I** (**10**), instead.

Compound (**8**) has been already recognized from *T. fruticans* L. (Coll and Tandrón 2005) but is reported for the first time in this study as a constituent of *T. polium*.

On the contrary, **picropolin** (**9**) had been initially identified as one of the bitter constituents of *T. polium* (Brieskorn and Pfeuffer 1967) and, as well as **teupolin I** (**10**), has been already recognized from *T. polium* L. (Malakov et al. 1979) and its subspecies i.e. *T. polium* subsp. *capitatum* (Fernandez et al. 1986). **Teupolin I** (**10**) has been also identified from other species of the genus such as *T. canadense* L. (Bruno et al. 1989), *T. bicolor* Sm. (Labbe et al. 1989) and *T. scorodonia* L. (Marco et al. 1982).

Neo-clerodane diterpenoids containing a β-substituted furan ring, are widely distributed in *Teucrium* genus and possess a pronounced protective action against herbivores predators. In fact, their antifeedant action has been extensively studied and confirmed (Bruno et al. 2002; Coll and Tandrón 2005; Piozzi et al. 2005; Aravind et al. 2010).

This antifeedant activity of *neo*-clerodanes may represent, indeed, the reason of their distribution and conservation in the studied genus.

On the other hand, they are also responsible of hepatotoxic effects (Loeper et al. 1994; Fiorentino et al. 2011; Gori et al. 2011; Pacifico et al. 2012) and, mainly due to this aspect, the traditional uses of this species is drastically diminished in the last years.

It should also be underlined that the presence of *neo*-clerodanes in the studied accession of *T. polium* resulted to be very low in respect to the other constituents. On the contrary, in one of our previous work (Venditti et al, 2017), on a sample from Northern Iran these compounds resulted to be the major constituents. In contrast with findings of previous morphological study on this species which revealed no environmental influence on taxonomical and morphological parameters (Bukhari et al, 2015), the results obtained in the present study may reveal instead an intraspecific variability for what concerns the production of the secondary metabolites and, at the same time, highlights the importance of the phytochemical analysis of the raw materials devoted to ethno-medicinal uses.

Another important chemo systematic aspect emerged from the study of this plant is about the total absence of iridoids which are considered to be taxonomic markers of this genus and of Lamiaceae themselves. It is noteworthy the fact that the chemotaxonomic markers of the family, harpagide and 8-*O*-acetylharpagide, previously identified in *T. polium* (Rizk et al. 1986) as well as in many other genera of the Lamiaceae such as *Ajuga* spp., *Melittis melissophyllum, Stachys* spp. (Venditti et al. 2013a; Venditti et al. 2013b; Venditti et al. 2014, Venditti et al. 2016; Venditti et al. 2016b; Frezza et al. 2016), were completely absent in our sample. The same thing resulted to happen for teucardoside, currently considered the chemotaxonomic marker of the genus since it has been already found in other *Teucrium* species (Essam et al., 1998). Such condition, the absence of iridoids, has already been observed in our previous study on a sample collected from a different population growing in the North of Iran (Venditti et al, 2017). The absence of such compounds, just like in the case of the variable content in *neo*-clerodane and just like already observed for the essential oil composition, may be due to both the climatic and ecological conditions of the collection site and to an intraspecific variability in the secondary metabolites production, which together generate different chemotypes.

Conclusions:

This study, performed on a sample of *T. polium* collected in Southern Iran, evidenced the presence of a major amount of phenolic components such as flavonoids and phenylethanoid glycosides, endowed with healthy properties, which may substantiate, on the molecular basis, the ancient ethno-medicinal uses of this species.

On the other hand, the presence of *neo*-clerodanes, even if in little amounts, was also relieved and these are known to possess hepatotoxic properties.

The co-presence of all these metabolites, with diametrically opposite effects, confirms the necessity to perform a deep phytochemical analysis on the plant materials collected for botanical purposes.

From the chemo systematic point of view, it is interesting to note that the studied sample did not contain iridoids currently considered as chemical markers for this species.

It is very likely the existence of several chemotypes within this genus which may synthesize or not iridoids.

Table 1. Occurrence of flavonoid aglycones in *Teucrium* species.

Species	Flavonoids
T. polium	cirsimaritin cirsiliol cirsilineol apigenin diosmetin
T. polium spp. *capitatum* (L.) Arcang. (syn. of *T. capitatum* L.)	apigenin cirsiliol diosmetin cirsimaritin cirsilineol
T. pilosum Decne. (syn. of *T. decaisnei* C.Presl)	cirsimaritin diosmetin apigenin
T. polium var. *pilosum* Decne. (syn. of *T. decaisnei* C.Presl)	cirsiliol
T. polium var. *alba* (= *T. polium* subsp. *album* (Poir.) Breistr. (syn. of *T. capitatum* L.)	cirsiliol
T. barbeyanum Asch. & Taub. ex E.J.Durand & Barratte	cirsiliol cirsimaritin cirsilineol apigenin
T. chamaedrys	cirsiliol cirsimaritin apigenin
T. montanum	apigenin diosmetin
T. alyssifolium Stapf	cirsiliol cirsilineol
T. orientale L. var. *orientale* (syn. of *T. orientale* L.)	cirsilineol
T. leucocladum Boiss	cirsimaritin

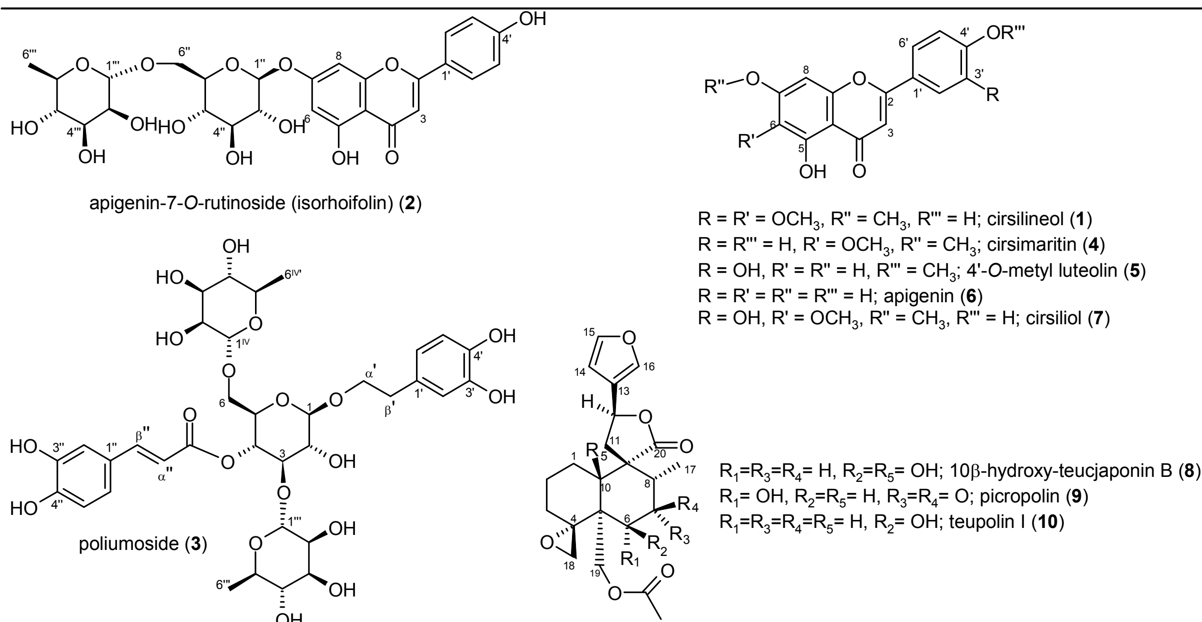

Figure 1. Compounds identified in *T. polium* from South Iran.

Competing interests

The authors declare that they have no competing interests.

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