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A NEW NEO-CLERODANE DITERPENOID FROM *TEUCRIUM POLIUM* LINN.

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ABSTRACT: *Teucrium polium* L. is a member of the Lamiaceae family and is represented in the Flora of Syria by two variety: *Teucrium polium* var. *angustifolium* and *Teucrium polium* var. *mollissimum*. *Teucrium polium* is a wild-growing flowering plant, found abundantly in Syria, and it is used traditional medicine for its diuretic, antipyretic, antispasmodic, tonic, anti-inflammatory, antihypertensive, anorexic, analgesic, antibacterial and anti-diabetic effects. Several reports have demonstrated a wide range of beneficial biological and pharmacological activities of the phenylethanoid, phenylpropanoid and flavonoid components, while the furano neo-clerodane diterpenoids present in germander have been implicated in the *in-vivo* hepatotoxicity of this botanical. Phytochemical studies of this plant have been carried out. Aerial parts of the plant were extracted with petroleum ether at room temperature, and then extract with methanol in Soxhlet, and finally extract with aqueous methanol at room temperature successively. Fractionation of the methanol extract by column chromatography and purification by crystallization yielded three known flavonoids cirsimartin, cirsiliol, and apigenin. The aqueous methanolic extract yielded one new neo-clerodane type diterpenoid, syrapolin I 1 (3, 12- diacetoxy - 4 α , 18 α ; 15, 16-diepoxy - 6 - oxo - neo - cleroda - 13 (16), 14- diene -7 α , 20 β - dihydroxy-19-hemiacetal). The structures of compounds were proposed based on spectroscopic methods IR, MS, and 1-D (^1H , ^{13}C , and DEPT) and 2-D (COSY, HETCOR, HMBC) NMR experiment, and comparison with closely related compounds.

INTRODUCTION: *Teucrium polium* (Family Lamiaceae) is one of the popular fragrant plants in Syria and is distributed throughout the country. In the Flora of Syria, this genus is represented by 21 species. *Teucrium polium* is a perennial shrub, 20-50 cm high, distributed widely in the dry and stony hills and deserts of almost all Mediterranean countries, South-Western Asia, Europe, and North Africa¹.

The plant releases a pleasant aromatic odor, and the flowers are small, in clusters and range from pink to white. In the folk medicinal traditions, this plant is used for its antibacterial, antispasmodic, anti-rheumatic, anti-diabetic and antipyretic activities. In an admixture with other powdered herbs, it is claimed to be therapeutic for peptic ulcer.

The biological activities of *T. polium* are widely reported, and it has been shown to possess anti-inflammatory², anti-nociceptive^{3, 4} activities. The aqueous extract of *Teucrium polium* aerial parts, given intra-peritoneally at dosages from 50 to 150 mg/kg for 10 days, reduced significantly the serum levels of cholesterol and triglycerides in hyperlipidemic rats⁵. Recently, the high insulinotropic and anti-hyperglycemic activity of its crude extract

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using both animal and isolated rat pancreatic islets has been evaluated⁶⁻⁸. Antibacterial activity against some Gram-positive and Gram-negative bacteria as well as antifungal activity against *Yarrowia lipolitica* and *Saccharomyces cerevisiae* has also been reported^{9,10}. Recently, cytotoxic, anticancer, and anti-mutagenic effects of ethanol and aqueous extracts of *T. polium* have been shown on various cell lines^{11,12,13}. *T. polium* extract contains selenium¹⁴ and has shown antioxidant activity like α -tocopherol. In particular, their antioxidant activities were evaluated through the use of several commonly accepted in vitro assays, which included DPPH scavenging (DPPH), reducing power (RP), xanthine oxidase inhibitor effect (XOI) and antioxidant activity in a linoleic acid system (ALP)¹⁵⁻²¹. The few adverse effects of *T. polium* have been reported which indicate the relatively safe nature of this medicinal herb²²⁻²⁷.

The composition of the essential oil of *T. polium* has been the subject of several investigations²⁸⁻³⁶. The naturally occurring neo-clerodane diterpenoids have attracted interest because of their biological activity as insect anti-feedants and as antifungal, antitumor and antimicrobial agents. Although, a large number of these compounds have been isolated from many plants in the last few years, the genus *Teucrium* is one of the richest sources of neo-clerodane diterpenes: more than 230 diterpenes have been described. Phytochemical investigations of *T. polium* have been shown that it contains a lot of diterpenes belong to neo-clerodane type³⁷⁻⁴⁵.

T. polium also rich in constituents such as flavonoids, iridoids and Phenylpropanoid glycosides with undoubted antioxidant properties^{18,46-50}. Our previous work on the aerial parts of *T. polium* L. var. *mollissimum* Hand-Mazz. led to the isolation of one new neo-clerodane diterpenes Syrapolin II, and two known compounds 6'-O-caffeoyl-8-O-acetylharpagide, clerosterol-3-O-glucoside⁵¹. In continuation of our studies on neo-clerodane diterpenoids from the *Teucrium* species, we have investigated *T. podium*, a small shrub which grows widely in Syria. From the methanolic extract and aqueous methanolic extract of the aerial parts of this plant we have isolated the new neo-clerodane diterpenoids Syraoiln I (1), beside to three new known flavonoides, Cirsimartin 2, Cirsiliol 3, and Apigenin 4.

MATERIALS AND METHODS:

Instrumentation: The ¹H and ¹³C NMR spectra were recorded on Bruker Ultra Shield 400 MHz spectrometer (faculty of Science, Al-Baath University, Homs, Syria) and reported in ppm. (δ) relative to TMS as internal standard and DMSO-*d*₆ as solvent. The IR spectra were measured on JASCO (FT-IR) - 410 spectrophotometer (Medico Medical Company, Homs, Syria). MS spectra were recorded on Shimadzu GCMS-QP 2010 (Syrian atomic energy commission, Damascus, Syria). Silica gel 60 F₂₅₄ plates (Merck) were used for analytical and preparative TLC. Silica gel S (Merck; Mesh 230-400) was used for column chromatography (CC), and all the chemicals were purchased from Merck.

Plant Material: *Teucrium polium* L. Amouda, Al-Hassaka, Syria in April 2008, and identified by Pro. Dr. Anwer Al-Khateeb, Department of Botany, College of Science, Damascus University, Damascus, Syria. A voucher specimen is available in the herbarium of Department of Botany in Damascus University.

Extraction and Isolation: Dried and finely powdered *Teucrium polium* L. aerial parts (4 kg) were extracted with petroleum ether at room temperature for 2 days, then filtrate and the residual plant re-extracted with methanol in Soxhlet. The methanolic extract (180 g) evaporated under reduced pressure and then extracted with diethyl ether. The diethyl ether extract (8 g) was chromatographed on silica gel column and eluted with n-hexane, n-hexan-CHCl₃ (90:10), n-hexan-CHCl₃ (50:50), gradient CHCl₃-MeOH, and pure MeOH, and the fractions collected as 25 ml.

Elution with CHCl₃-MeOH (90:10) affords 160 fractions. Fractions (92-100) gave 71 mg of an impure compound which was crystallized in dichloromethane to give 38 mg of compound 2, and Fractions (122-124) gave 64 mg of an impure compound which was crystallized in dichloromethane to give 29 mg of compound 3. Elution with CHCl₃-MeOH (80:20) gave 48 mg residue which was crystallized in a mixture of acetone-methanol to give 22 mg of pure compound 4. The plant residue from methanolic extract then re-extracted with the mixture of MeOH-H₂O (70:30) at room temperature, and the filtrate was

evaporated in vacuum, and during this evaporation, the white precipitate was accumulated, we filtrated it and washed with methanol to give 80 mg of pure compound 1.

RESULTS AND DISCUSSION: Syrapolin I (1) **Fig. 1** gave a molecular ion peak in its EI-mass spectrum at m/z 478, in agreement with the molecular formula $C_{24}H_{30}O_{10}$. The other prominent

peaks were found to occur at m/z 460 $[M-H_2O]^+$, 418 $[M-AcOH]^+$, 135, 122, 105(100), 94, 91, 81, 77, 55, 43.

The IR spectrum of (1) showed absorptions of furan ring (3141.5, 3124.1, 1504.2, 874.6 cm^{-1}), hydroxyl (3381.5 cm^{-1} , br), tow acetates (1754.9, 1731.8, 1280.5, 1239.0 cm^{-1}), and a strong band for a carbonyl group (1713.4 cm^{-1}).

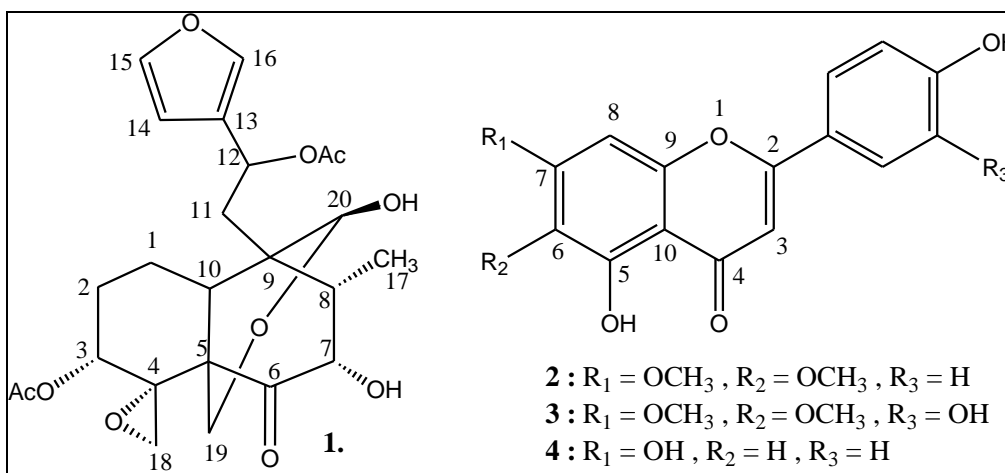


FIG. 1: STRUCTURE OF COMPOUNDS 1, 2, 3, 4

The data from the ^{13}C -NMR spectrum **Table 1** display 24 signals. The multiplicities of carbon signals were determined by the DEPT experiment. Taking into account the results from our comprehensive 1D and 2D-NMR studies and previous knowledge derived from metabolites isolated from the genus *Teucrium*^{39, 51-53} it is evident that (1) possesses a highly oxidized neoclerodane nucleus. The 1H -NMR spectrum **Table 1** of compound (1) showed a *dd* at δ 6.56 ($J = 0.8, 1.6$ Hz, H-14), a broad singlet at δ 7.71 (H-15), and a triplet at δ 7.63 ($J = 1.7$ Hz, H-16) were readily assigned to a terminal furan ring. Also, the 1H -NMR spectrum showed two AB system (δ 2.95, 4.14 and 2.96, 2.81) which we have assigned to H-19 and H-18 respectively.

The broad doublet at δ 5.83 and the doublet at 4.87 were assigned to H-12 and H-20, respectively. The 1H -NMR spectrum also showed two doublet at δ 5.03 (5.6 Hz), 6.47 (4.2 Hz) which were not connected to any carbon atoms in HETCOR spectrum were assigned to two hydroxyl group, and disappeared from 1H -NMR spectrum when recorded in DMSO with few drops of D_2O . Detailed examination of 1H -NMR spectrum indicated the presence of 1H - 1H spin system which

could be traced from the secondary methyl protons δ 1.09 (*d*, $J = 6.8$ Hz, 3H-17) to δ 1.66 (*q*, $J = 6.4$ Hz, H-8) and from there to an oxymethine proton at δ 4.25 (*dd*, $J = 5.6, 9.9$ Hz, H-7). Mutual coupling with the signal at δ 5.03 (*d*, $J = 5.6$ Hz, OH) suggested by the common J value, was confirmed by a cross peak in the 1H -NMR, 2D COSY spectrum, and supported the presence of a hydroxyl group at C-7 with α configuration (equatorial). As expected, no cross peak was observed in the HETCOR spectrum for a carbon resonance and proton signal at δ 5.03, but in the HMBC spectrum, cross peaks were observed for C-6, C-8, and C-7. The HMBC spectrum also showed cross peaks between the signal at δ 6.47 (*d*, $J = 4.2$ Hz, C20-OH) and C-20, C-9, and C-10. The 1H -NMR spectra also show tow singlet at δ 1.90, and 2.03 indicate to the tow CH_3 in acetate groups.

The ^{13}C -NMR **Table 1** and DEPT spectra confirmed the presence of a furan ring (δ 126.70, C-13; 109.38, C-14; 140.37, C-15 and 144.31, C-16), a carbonyl group (δ 208.23, C-6), tow acetate (δ 169.90 COMe; 21.42, COMe, and 170.24 COMe; 21.70, COMe), one methyl signal (δ 13.68, C-17) and two oxygen-substituted methylene signals for the C-18 and C-19 at δ 52.39 and 54.00

respectively, three oxygen-substituted methine signals for the C-3, C-7, C-12 and C-20 at δ 72.97, 78.85, 65.23 and 93.29 respectively. On the basis of these facts, the structure of (1) was established as 3, 12- diacetoxy- 4 α ,18 α ;15,16- diepoxy- 6- oxo-neo-cleroda-13(16),14-diene-7 α ,20 β -dihydroxy-19-hemiacetal.

TABLE 1: ^{13}C -NMR AND ^1H -NMR DATA OF 1 (400 MHz, DMSO- d_6)

No.	C	DEPT	HETCOR
1	19.05	CH ₂	2.17 <i>m</i> (5.2 Hz)
2	26.87	CH ₂	a 1.62 <i>brd</i> (6.4 Hz) b 2.14 <i>m</i> (5.2 Hz)
3	72.97	CH	4.29 <i>d</i> (6.1 Hz)
4	55.93	C	
5	48.20	C	
6	208.23	C	
7	78.85	CH	4.25 <i>dd</i> (5.6, 9.9 Hz)
8	46.90	CH	1.66 <i>q</i> (6.4 Hz)
9	41.12	C	
10	40.77	CH	2.20 <i>d</i> (4.4 Hz)
11	35.73	CH ₂	a 1.56 <i>dd</i> (16.2, 2.4 Hz) b 2.45 <i>dd</i> (12, 16 Hz)
12	65.23	CH	5.83 <i>br d</i> (8 Hz)
13	126.70	C	
14	109.38	CH	6.56 <i>dd</i> (0.8, 1.6 Hz)
15	140.37	CH	7.71 <i>brs</i>
16	144.31	CH	7.63 <i>t</i> (1.7 Hz)
17	13.68	CH ₃	1.09 <i>d</i> (6.8 Hz)
18	52.39	CH ₂	a 2.81 <i>d</i> (4.7 Hz) b 2.96 <i>d</i> (4.7 Hz)
19	54.00	CH ₂	a 2.95 <i>d</i> (12.3 Hz) b 4.14 <i>d</i> (12.4 Hz)
20	93.29	CH	4.87 <i>d</i> (4.3 Hz)
CH ₃ CO	21.42	CH ₃	1.88 <i>s</i>
CH ₃ CO	21.70	CH ₃	2.04 <i>s</i>
CH ₃ CO	169.90		
CH ₃ CO	170.24		
		OH	5.03 <i>d</i> (5.6 Hz)
		OH	6.47 <i>d</i> (4.2 Hz)

Compound (2) was obtained as a yellow granular powder and exhibiting a positive ferric chloride test and magnesium hydrochloric acid test. Compound (2) gave a molecular ion peak in its EI-mass spectrum at m/z ; $M = 314$ (100%), and M^{+1} (11%) in agreement with the molecular formula C₁₇H₁₄O₆. IR spectrum of (2) showed absorption band for hydroxyl groups 3300 cm⁻¹, α,β -unsaturated carbonyl carbon 1640 cm⁻¹, and aromatic double bond 1595 cm⁻¹ functionalities. The UV spectrum of (2) exhibited absorption maxima at 331 (Band I) and 275 nm (Band II) (in MeOH), bathochromic shifts of 67, 3 and 4 nm with NaOMe, NaOAc and AlCl₃ in Band I, respectively. These data revealed

that (2) has a flavonoid type structure. The ^1H -NMR spectrum of (2) **Table 2** showed a characteristic low-frequency signal at δ 12.90 (*s*, 5-OH) assignable to aromatic hydroxyl signal hydrogen bonded to carbonyl at C-5 of a flavonoid. Two *ortho*-coupled aromatic protons at δ 7.92 (1H, *d*, $J = 8.1$ Hz) and δ 6.92 (1H, *d*, $J = 8.1$ Hz) were diagnostic for a C-2'/C-6' and C-3'/C-5' oxygenated ring B. The ^1H NMR spectrum showed two aromatic proton signals at (δ 6.86, *s*, H-8) and (δ 6.80, *s*, H-3). The ^1H -NMR also showed two singlet signal at δ 3.72 (*s*, 3H) and δ 3.90 (*s*, 3H) indicate the presence of two methoxy group. In ^{13}C -NMR spectra **Table 2** and DEPT-135, the signals at δ 164.53, 103.15, 182.10, 152.58 and 105.56 were typical of C-2, C-3, C-4, C-9 and C-10 of a flavonoid moiety. The position of two methoxy groups was authenticated through the HMBC spectrum between methoxy protons at δ 3.72 and C-6, and δ 3.90 and C-7. By comparison of ^1H - and ^{13}C -NMR chemical shifts with those reported in the literature, the flavonoid skeleton were in agreement with those of cirsimartin⁵⁴.

Compound (3) **Fig. 1** isolated as a pale yellow amorphous powder. The UV spectrum of (3) in methanol showed three peaks at 274, 348 and 447 nm. The UV spectrum of (3) with NaOMe showed peaks at 266 and 408 nm, and with NaOAc at 254 and 338 nm, and with AlCl₃ at 271 nm. These data revealed that (3) has a flavonoid type structure. The IR spectrum of (3) showed absorption band for hydroxyl groups 3410 cm⁻¹, carbonyl group 1647 cm⁻¹ (C = O α,β -unsaturated), and an aromatic double bond at 1580 cm⁻¹. Compound (3) gave a molecular ion peak in its EI-mass spectrum at m/z 330 (100%), in agreement with the molecular formula C₁₇H₁₄O₇.

The ^1H -NMR spectrum of (3) **Table 2** showed a characteristic low-frequency signal at δ 12.91 (*s*, OH) assignable to aromatic hydroxyl. Two *ortho*-coupled aromatic protons at δ 7.44 (1H, *d*, $J = 8.1$ Hz) and δ 6.90 (1H, *d*, $J = 8.1$ Hz) were diagnostic for a C-5' and C-6' oxygenated ring B. The ^1H -NMR spectrum showed three aromatic proton signals at (δ 6.85, *s*, H-8), (δ 6.71, *s*, H-3) and (δ 7.45, *s*, H-2'). The ^1H -NMR also showed two singlet signal at δ 3.72 (*s*, 3H) and δ 3.91 (*s*, 3H) indicate the presence of two methoxy group. In ^{13}C -NMR spectrum **Table 2** and DEPT-135, the

signals at δ 164.77, 103.18, 183.64, 152.58 and 105.54 were typical of C-2, C-3, C-4, C-9 and C-10 of a flavonoid moiety. The position of two methoxy groups was authenticated through the HMBC spectrum between methoxy protons at δ 3.72 and

C-6, and δ 3.91 and C-7. By comparison of ^1H - and ^{13}C -NMR chemical shifts with those reported in the literature, the flavonoid skeleton were in agreement to those of Cirsiliol⁵⁵.

TABLE 2: ^{13}C -NMR AND ^1H -NMR DATA OF COMPOUND (2), (400 MHz, DMSO- d_6)

No.	2		3		4	
	C	H	C	H	C	H
2	164.53	-	164.77	-	164.77	-
3	103.15	6.80, 1H, <i>s</i>	103.18	6.76, 1H, <i>s</i>	103.32	6.71, 1H, <i>s</i>
4	182.10	-	183.64	-	182.25	-
5	153.11	-	153.13	-	164.23	-
6	132.33	-	132.35	6.18, 1H, <i>d</i> , <i>J</i> = 2.09 Hz	99.44	-
7	159.09	-	159.11	-	164.95	-
8	92.00	6.86, 1H, <i>s</i>	91.95	6.85, 1H, <i>s</i>	94.54	6.48, 1H, <i>d</i> , <i>J</i> = 2.09 Hz
9	152.58	-	152.57	-	157.86	-
10	105.56	-	105.54	-	104.14	-
1'	121.61	-	121.94	-	121.68	-
2'	129.01	7.92, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	113.94	7.45, 1H, <i>s</i>	128.99	7.92, 1H, <i>d</i> , <i>J</i> = 8.9 Hz
3'	116.47	6.92, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	146.30	-	116.50	6.92, 1H, <i>d</i> , <i>J</i> = 8.9 Hz
4'	161.79	-	150.38	-	161.99	-
5'	116.47	6.92, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	116.49	6.90, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	116.50	6.92, 1H, <i>d</i> , <i>J</i> = 8.9 Hz
6'	129.01	7.92, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	119.59	7.44, 1H, <i>d</i> , <i>J</i> = 8.1 Hz	128.99	7.92, 1H, <i>d</i> , <i>J</i> = 8.9 Hz
OCH ₃	60.53	3.72, 3H, <i>s</i>	60.58	3.72, 3H, <i>s</i>		12.98, <i>s</i>
OCH ₃	56.91	3.90, 3H, <i>s</i>	56.93	3.91, 3H, <i>s</i>		
C4'-OH		10.40, <i>br s</i>		12.91, <i>s</i>		
C5-OH		12.90, <i>s</i>				

Compound (4) **Fig. 1** isolated as a yellow granular powder. The UV spectrum of (4) in methanol showed three peaks at 266 and 334 nm. The UV spectrum of (4) with NaOMe showed peaks at 274, 322 and 390 nm and with NaOAc at 276, 300 and 378 nm, and with AlCl₃ at 277, 302, 338 and 384 nm. These data revealed that (4) has a flavonoid type structure. The IR spectrum of (4) showed absorption band for hydroxyl groups 3352 cm⁻¹, α,β -unsaturated carbonyl group 1647 cm⁻¹, and an aromatic double bond at 1602 cm⁻¹. Compound (4) gave a molecular ion peak in its EI-mass spectrum at *m/z* 270 (100%), in agreement with the molecular formula C₁₅H₁₀O₅.

The ^1H -NMR spectrum of (4) **Table 2** showed two *ortho*-coupled aromatic protons at δ 7.92 (1H, *d*, *J* = 8.9 Hz) and δ 6.92 (1H, *d*, *J* = 8.9 Hz) were diagnostic for a C-2'/C-6' and C-3'/C-5' oxygenated ring B. The ^1H -NMR spectrum of (4) **Table 2** also showed two *meta*-coupled aromatic protons at δ

6.48 (1H, *d*, *J* = 2.09 Hz) and δ 6.18 (1H, *d*, *J* = 2.09 Hz) were diagnostic for a C-8 and C-6 oxygenated ring A. The ^1H -NMR also showed one singlet signal at δ 6.76 (*s*, 1H) for C-3. In ^{13}C -NMR spectrum **Table 2** and DEPT-135, the signals at δ 164.77, 103.32, 182.25, 157.86 and 104.14 were typical of C-2, C-3, C-4, C-9 and C-10 of a flavonoid moiety. Analysis of the ^1H -NMR, ^{13}C -NMR, COSY, HETCOR, and HMBC experiments indicated that this compound bears a flavonoid skeleton, which was identified as Apigenin, by comparison of ^1H - and ^{13}C -NMR chemical shifts with those reported in the literature⁵⁶.

CONCLUSION: Phytochemical study of the aerial parts of *Teucrium polium* resulted in the isolation of four compounds, a new *neo*-clerodane diterpenoid (1), and three known flavonoids. The known flavonoids were identified as Cirsimartin (2), Cirsiliol (3), and Apigenin (4). The structures

were determined by physical, chemical and spectral techniques.

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CONFLICT OF INTEREST: Nil

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