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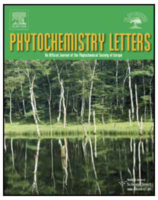

New sesterterpenoids and other constituents from *Salvia dominica* growing wild in Jordan

Mohammed R. Hasan[a], Hala I. Al-Jaber[b,*], Mahmoud A. Al-Qudah[c], Musa H. Abu Zarga[a,**]

[a] Department of Chemistry, Faculty of Science, The University of Jordan, Amman, Jordan
[b] Department of Physics and Basic Sciences, Faculty of Engineering Technology, Al-Balqa Applied University, Marka, Jordan
[c] Department of Chemistry, Faculty of Science, Yarmouk University, Irbid, Jordan

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ABSTRACT

A new nor-oleanane triterpene 24-nor-4(23)-12-oleanadien-2α,3α,28-triol (**1**) and two new sesterpenes salvidominicolide A (**2**), salvidominicolide B (**3**) together with fifteen known compounds were isolated from *Salvia dominica* L. growing wild in Jordan. The known compounds comprised six flavones, three triterpenes, one diterpene, one sesterterpene, two oxygenated monoterpenes, one sterol glucoside and one flavone glucoside. The isolated compounds were elucidated by extensive spectroscopic methods including NMR (1D and 2D), UV, IR and MS (HRMS).

1. Introduction

Salvia is one of the largest genera belonging to the mint family Lamiaceae (formerly known as Labiatae). *Salvia* plants are famous for their medicinal and culinary properties since ancient times. Many plants belonging to this genus are known for their anti-inflammatory, cytotoxic and anti-HIV-activities (Wu et al., 2012). This genus is known to be rich in flavonoids (Lu and Foo, 2002), diterpenoids (Kabouche and Kabouche, 2008), tritperpenoids (Al-Jaber et al., 2012), sesterterpenoids (Dal Piaz et al., 2009), phenolic compounds (Al-Qudah et al., 2014) and other compounds. It's worth mentioning that, *Salvia* is the only genus of the Lamiaceae family that produces sesterterpenes (Moghaddam et al., 2010).

Twenty five *salvia* species have been recorded in the flora of Jordan including *Salvia dominica* (Al-Eisawi, 2013). The plant is a perennial herb, shrubby, woody at the base, 20–30 cm long with many basal hairy and aromatic branches. Leaves are about 3–9 cm long, while the flowers are about 1.5–2 cm long, cream colored with yellow lower lip. This plant is known to grow wild in the Mediterranean biogeoraphical zone and flowers during the spring season from April to June (El-Eisawi, 1998). In Jordan, *S. dominica* is used as anti-colic and astringent plant remedy in the treatment of cold, stomach pain and indigestion (Feinbrun-Dothan, 1978). The plant is also known to produce edible galls (Al-Eisawi, 1998, 1982; Feinbrun-Dothan, 1978).

A thorough literature survey revealed that the plant has been investigated for its volatile (Abdallah et al., 2013) and nonvolatile (Dal Piaz et al., 2009) chemical constituents and evaluated for its antiproliferative activity against several cancer cell lines including MCF-7 and T47D (Abu-Dahab et al., 2012).

As part of our continuous effort in investigating the chemical constituents of flora of Jordan (Al-Jaber et al., 2012; Al-Qudah et al., 2015; Al-Qudah et al., 2014), we report here the isolation and characterization of one new 24-nor-oleanane triterpenoid (**1**) and two new sesterterpenes (**2** and **3**) in addition to fifteen known compounds from *S. dominica*. All these compounds were characterized on the basis of extensive spectroscopic data including 1D and 2D NMR, UV, IR and HRMS.

2. Results and discussion

The crude methanol extract of the whole plant material was partitioned into aqueous methanol, hexane, butanol and water extracts according to the procedure described in the experimental section. The aqueous methanol and the butanol extracts were subjected to successive chromatographic separations to afford eighteen compounds, three of which were new. The new

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* Corresponding author. Tel.: +962 6 4790333 – 4790359/ext. 108.
** Corresponding author. Tel.: +962 6 5355000/ext. 22131.
E-mail addresses: rhhjaber@yahoo.com (H.I. Al-Jaber), musaaz@ju.edu.jo (M.H. Abu Zarga).

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compounds were 24-nor-4(23)-12-oleanadien-2α,3α,28-triol (**1**), salvidominicolide A (**2**) and salvidominicolide B (**3**). The fifteen known compounds were identified as salvigenin (Chaturvedula and Prakash, 2013) pectolinangenin (Al-Jaber et al., 2012), oleanolic acid (Seebacher et al., 2003), ursolic acid (Bozan et al., 2002), genkwanin (Wagner et al., 1976), sclareol (Forster et al., 1985), maslinic acid (Weis and Seebacher, 2002), apigenin (Chaturvedula and Prakash, 2013), β-sitosteryl glucoside (Rahman et al., 2009), salvisyriacolide (Rustaiyan and Sadjadi, 1987), (3R,6R) 2,6-dimethyl-7-octene-2,3,6-triol (Williams et al., 1980), (3S,6R) 2,6-dimethyl-7-octene-2,3,6-triol (Williams et al., 1980), luteolin (Chaturvedula and Prakash, 2013), nepetin (Shim et al., 2012) and luteolin 7-O-glucoside (Markham et al., 1978). It is worth mentioning that the compounds pectolinangenin, oleanolic acid, ursolic acid, sclarcol, maslinic acid, nepetin and luteolin 7-O-glucoside are reported here for the first time from the plant while compounds (3R,6R) 2,6-dimethyl-7-octene-2,3,6-triol and (3S,6R) 2,6-dimethyl-7-octene-2,3,6-triol are reported for the first time from the genus *Salvia*. Fig. 1 shows the structures of the new isolated compounds.

Compound **1** (Fig. 1) was obtained as a white crystalline solid. Its molecular formula was deduced as $C_{29}H_{46}O_3$ based on its HRMS which showed a molecular ion peak M^+ at *m*/*z* 465.3343 (calcd. for 465.3345). Its NMR spectroscopic data revealed interesting characteristics of a 24-nor-oleanane skeleton similar to compounds 2α,3α-dihydroxy-24-nor-4(23), 12-oleanan-28-oic acid (Al-Jaber et al., 2012) and 2α,3α,16α-trihydroxy-24-nor-4(23), 12-oleandien-28-oic acid (Cioffi et al., 2008) that have previously been reported from *S. palaestina.*

The ^1H NMR of compound **1** (Table 1) along with the 2D COSY and HMQC spectra revealed the presence of five methyl singlets at δ_H 0.68, 0.80, 0.89 (2Me) and 1.11, a trisubstituted double bond proton resonating at δ_H 5.19 (br s, H-12), an exocylic methylene protons at δ_H 4.56, 4.93 (H-23α, H-23β), one hydroxymethylene group at δ_H 3.56 (br s, 2H-28) and two vicinal hydroxymethine moieties at δ_H 3.48 (ddd, *J* = 5.7, 11.5, 15.6, H-2), and δ_H 3.99 (br d, *J* = 3.0, H-3). The oleanane skeleton of compound **1** was confirmed from the doublet of doublet signal resonating at δ_H 2.78 (*J* = 2.8, 13.2) which was unambiguously assigned to H-18. The *J* values of H-2 and H-3 are consistent with the *cis* configuration of OH-2 and OH-3 while the downfield shift values of C-2 (δ 68.6) and C-3 (δ 75.6) explains the α-stereochemistry of both hydroxyl groups.

Two-dimensional NMR experiments including ^1H-^1H COSY, HMQC and HMBC were used to assign the relationships between ^1H and ^{13}C NMR resonances. The position of the exocyclic methylene was confirmed through the HMBC long range correlations observed between H-23 and each of C-3 (δ_H 3.99, δ_C 75.6) and C-5 (δ_H 2.08, δ_C 44.6). Moreover, the long range correlations observed in the HMBC spectrum between all methyl groups (Me-25, Me-26, Me-27, M-29 and Me-30) and their neighboring carbon atoms helped in locating those methyls and assigning the oxygenated methylene to C-28 of the triterpenoidal skeleton. Fig. 2 illustrates the key HMBC and COSY correlations observed for compound **1**. Based on these data, compound **1** was identified as 24-nor-4(23)-12-oleanadien-2α,3α,28-triol.

Table 1
^1H (500 MHz) and ^{13}C (125 MHz) NMR data (δ in ppm) of compound **1** (in DMSO-d_6).

Position	δ_C	δ_H (m, *J*, Hz)
1	42.9	1.22 (1H, m); 1.54 (1H, dd, *J* = 4.5, 12.4)
2	68.6	3.48 (1H, ddd, *J* = 5.7, 11.5, 15.6)
3	75.6	3.99 (1H, d, *J* = 3.0)
4	152.2	–
5	44.6	2.08 (1H, br t, *J* = 7.2)
6	20.4	0.85 (1H, m); 1.36 (1H, m)
7	31.4	1.52 (2H, m)
8	39.5	–
9	45.1	1.68 (1H, dd, *J* = 7.1, 11.7)
10	37.8	–
11	23.1	1.51 (2H, m)
12	121.9	5.19 (1H, brs)
13	145.0	–
14	42.1	–
15	27.5	1.02 (1H, m); 1.69 (1H, m)
16	24.2	1.83 (1H, m); 1.95 (1H, m)
17	45.9	–
18	41.5	2.78 (1H, dd, *J* = 2.8, 13.2)
19	46.2	1.08 (2H, br d, *J* = 2.6)
20	31.0	–
21	33.9	1.12 (1H, m)
22	32.6	1.36 (1H, m); 1.65 (1H, m)
23	109.3	4.56 (1H, brs); 4.93 (1H, brs)
Me-25	14.2	0.68 (3H, s)
Me-26	17.6	0.80 (3H, s)
Me-27	26.1	1.11 (3H, s)
28	70.2	3.56 (2H, br s)
Me-29	33.3	0.89 (6H, s)
Me-30	23.9	

Compound **2** was isolated as a white crystalline solid. Its molecular formula was established based on its ^{13}C NMR spectrum as well as the HRMS which showed a molecular ion peak at $[M]^+$ *m*/*z* 464.27739 corresponding to the molecular formula $C_{26}H_{40}O_7$ (calcd. for 464.27740) and indicating a sesterterpene. The IR spectrum of this compound showed intense absorption peaks at 1736 and 3424 cm^{-1} indicating the presence of an α,*β*-unsaturated lactone carbonyl moiety in addition to free OH functional groups.

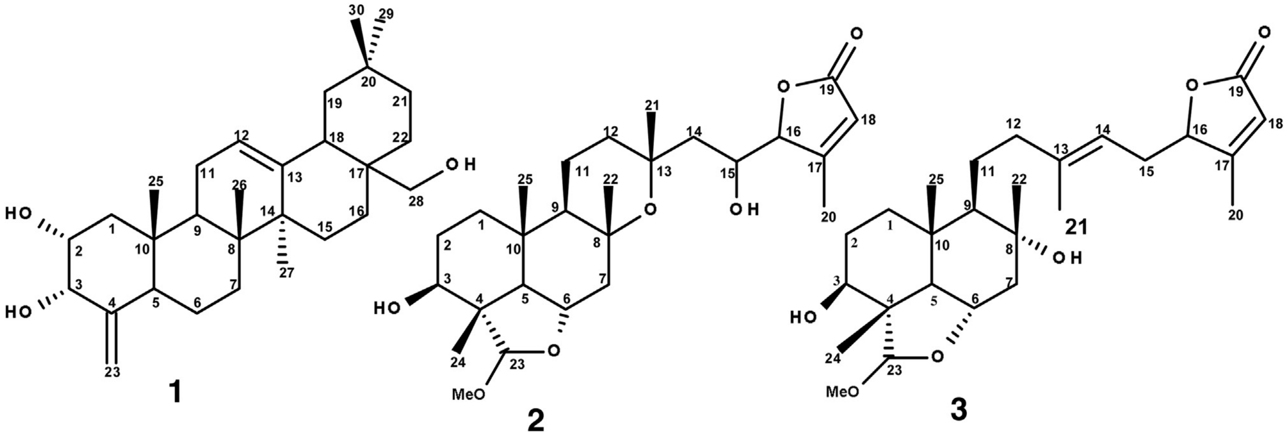

Fig. 1. Structures of new compounds isolated from *S. dominica* from Jordanian origin.