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New tetranorlabdanoic acid from aerial parts of *Salvia aethiopis*

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Abstract

Salvia aethiopis is a perennial plant native to Eurasia and known by the common names Mediterranean sage or African sage. This plant has been used in Iranian medicine as a carminative and tonic. The ethanolic extract of aerial part of *S. aethiopis* exhibited moderate to weak activity towards delta and kappa opioid receptors (46.3 and 45.3% displacement, respectively). Chromatographic purification of the ethanolic extract on silica gel column led to isolation of one new: 3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (**I**) and three known compounds: sesquiterpene spathulenol (**II**), β -sitosterol (**III**) and β -sitosterol-3-O-glucoside (**IV**). The structures of all isolated compounds were elucidated by their NMR (1D and 2D) and MS spectral data. All the fractions and isolated compounds were tested for cannabinoid and opioid receptor binding assays.

Graphical Abstract

Keywords

Salvia aethiopis; isolation; labdane; sesquiterpene; sterol

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Disclosure statement

No potential conflict of interest was reported by the authors.

1. Introduction

The genus *Salvia* is the largest genus in mint family (Lamiaceae). This genus includes nearly 1000 species which are widely distributed all over the world. Genus *Salvia* is a rich source of essential oils, flavonoids and terpenoids (Al-Aboudi et al. 2015; Hussain et al. 2016; Jassbi et al. 2016; Salimikia et al. 2016; Tabatabaei et al. 2017). This genus is reported for antioxidant, antimicrobial and antiviral activities (Jassbi et al. 2016; Moridi Farimani & Abbas-Mohammadi 2016). Plants belonging to genus *Salvia* are well known in folk medicine to treat epilepsy, aches, colds, bronchitis and menstrual disorders (Velickovic et al. 2002; Tajbakhsh et al. 2007; Güllüce et al. 2006).

Salvia aethiopis is a perennial plant, known by the common names Mediterranean sage or African sage. In the United States, it is best known as a noxious weed (Dennis 1980). It was probably introduced to North America as a contaminant of alfalfa seed but natives to Eurasia. Major chemical constituents of *S. aethiopis* are diterpenes and sesterpenes (Boya & Valverde 1981; Rodríguez et al. 1984; Hernández-Pérez et al. 1999; Ulubelen & Tan 1999; Malafronte et al. 2008). In continuation to our search on isolation of cannabinoid and opioid receptor active constituents from *Salvia* species (Srivedavyasasri et al., 2016) and less literature reports on this plant initiated us to work on isolation of chemical components from *S. aethiopis*.

2. Results and discussion

Compound **I** was obtained as a yellow gum (5 mg) and its high resolution FTMS-ESI showed a molecular ion at m/z 325.2004 $[M-H]^-$ (calcd for $C_{18}H_{29}O_5$ 325.2016). The 1H NMR spectrum ($CDCl_3$, 500 MHz) of compound **I** exhibited four methyl singlets at δ 0.79, 0.82, 0.94 and 1.48, which were assigned to the tertiary C-19, C-20, C-18 and C-17 methyl protons, respectively. One down field methyl singlet at δ 1.87 was assigned to the O-acetyl methyl protons at C-8. A characteristic downfield broad singlet at δ 3.35 attributes to a proton at C-3 position.

The ^{13}C NMR spectrum of **I** ($CDCl_3$, 100 MHz) showed resonances for 18 carbon atoms including five methyl, five methylene, three methine, three quaternary carbons and two carbonyl carbons. The downfield resonances at δ 178.41 and 170.24 were assigned to carbonyl carbon of acid and an ester, respectively. Two carbons at δ 86.29 (quaternary) and 75.71 (methine) were assigned to the oxygenated carbons C-8 and C-3, respectively. The resonances at δ 28.33, 22.60, 19.89 and 15.65, were ascribed to the methyl carbons C-18, C-19, C-17 and C-20, respectively. The methyl carbon at δ 21.95 was assigned to methyl group in O-acetate at C-8 position. The HMBC spectrum of compound **I** (Figure 1) showed the following correlations: acetyl methyl protons at δ 1.87 showed correlations with acetyl carbonyl at δ 170.24. The methyl protons at C-17 (δ 1.48) showed correlations with C-7 (δ 38.84), C-8 (δ 86.29) and C-9 (δ 55.02). The C-18 proton (δ 0.94) showed correlations with C-3 (δ 75.71), C-4 (δ 37.42), C-5 (δ 48.03) and C-19 (δ 22.60). The methyl protons at C-19 (δ 0.79) showed correlations with C-3 (δ 75.71), C-4 (δ 37.42), C-5 (δ 48.03) and C-18 (δ 28.33). The methyl protons at C-20 (δ 0.82) proton showed correlations with C-1 (δ 32.10),

C-5 (δ 48.03), C-9 (δ 55.02) and C-10 (δ 38.44). H-9 (δ 2.27) showed a weak correlation with C-12 (δ 178.41). The major COSY relations were observed in between H-2 and H-3, H-8 and H-11. Based on the key correlation in the NOESY spectrum between proton at C-3 (δ 3.35) and methyl C-20 (δ 0.82), and comparing with the published data of methyl ester of compound **I** (Gonzalez et al. 1989), hydroxyl group at C-3, orientation was determined to be alpha (α). The overall NMR data were in good agreement with a tetranorlabdan type diterpene and is similar to published compound methyl-3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oate, except the absence of methyl ester at C-12 position (Gonzalez et al. 1989). Hence, compound **I** could be identified as 3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (Figure 1) and this is the first time to be reported from nature.

The structure of isolated compounds **II**, **III** and **IV** were proved by comparing their NMR data with literature, to be sesquiterpene spathulenol (Vieira et al. 2013), β -sitosterol and β -sisterol-3-O-glucoside (Rai et al. 2006). Ethanolic extract showed moderate to weak activity towards CB1 (37.0% inhibition), Delta (46.3% inhibition) and Kappa (45.3% inhibition) receptors. DCM extract showed moderate to weak activity towards Delta receptor (35.7% inhibition). None of the isolated compounds showed cannabinoid and/or opioid receptor activity.

2.1. 3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (**I**)

White amorphous powder, FTMS-ESI m/z : 325.2004 $[M-H]^-$ (calcd for $C_{18}H_{29}O_5$ 325.2016). 1H NMR (500 MHz, $CDCl_3$): δ 2.73 (1H, m, H-7a), 3.35 (1H, br s, H-3), 2.34 (1H, m, H-6a), 2.27 (1H, m, H-9), 1.91 (1H, m, H-2a), 1.87 (3H, s, CH_3CO-), 1.71 (1H, m, H-7b), 1.59 (1H, m, H-2a), 1.56 (1H, m, H-11a), 1.55 (2H, m, H-1), 1.53 (1H, m, H-5), 1.48 (3H, s, H-17), 1.28 (1H, m, H-11b), 1.26 (1H, m, H-6b), 0.94 (3H, s, H-18), 0.82 (3H, s, H-20), 0.79 (3H, s, H-19). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.41 (C-12), 170.24 (CH_3CO-), 86.29 (C-8), 75.71 (C-5), 55.02 (C-9), 48.03 (C-5), 38.84 (C-7), 38.44 (C-10), 37.42 (C-4), 32.10 (C-1), 29.75 (C-11), 28.33 (C-18), 24.99 (C-2), 22.60 (C-19), 21.95 (CH_3CO-), 19.89 (C-17), 19.52 (C-6), 15.65 (C-20).

3. Conclusions

Ethanolic extract of aerial parts of *S. aethiopsis* showed moderate to weak activity towards delta and kappa opioid receptors (46.3 and 45.3% displacement, respectively). Bioassay guided fractionation and purification yielded four compounds (**I–IV**): 3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (**I**, new), sesquiterpene spathulenol (**II**), sitosterol (**III**) and sitosterol-3-O-glucoside (**IV**). Compound **I** is a new natural product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
3 α -hydroxy-8 α -acetoxy-13,14,15,16-tetranorlabdan-12-oic acid (I).