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Triterpenoid saponins from *Scabiosa stellata* collected in North-eastern Algeria

Meryem Lehbili [a, b], Abdulmagid Alabdul Magid [b, *], Ahmed Kabouche [a], Laurence Voutquenne-Nazabadioko [b], Hamid Morjani [c], Dominique Harakat [d], Zahia Kabouche [a]

[a] Université des frères Mentouri-Constantine, Département de chimie, Laboratoire d'Obtention des Substances Thérapeutiques (LOST), Campus Chaabet-Ersas, 25000, Constantine, Algeria
[b] ICMR-UMR CNRS 7312, Groupe Isolement et Structure, Campus Sciences, Bât. 18, BP 1039, 51687, Reims, France
[c] MEDyC UMR CNRS 7369, URCA, Faculté de Pharmacie, SFR CAP Santé, 1, rue du Maréchal-Juin, 51096, Reims, France
[d] Service Commun d'Analyses, Institut de Chimie Moléculaire de Reims (ICMR), CNRS UMR 7312, Bat. 18 B.P. 1039, 51687, Reims, Cedex 2, France

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ABSTRACT

Eight undescribed triterpenoid saponins, scabiostellatosides A-H, together with three known compounds were isolated from the whole plant of *Scabiosa stellata* L. Their structures were established by spectroscopic analyses (1D, 2D-NMR and HRESIMS) and chemical methods. Scabiostellatosides A-H were evaluated for their cytotoxicity against human fibrosarcoma cell line (HT1080). Scabiostellatoside F, a heptasaccharide derivative of oleanolic acid, exhibited moderate cytotoxicity against HT1080 cell line with IC_{50} value of 12.0 μM.

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1. Introduction

Scabiosa stellata L., known as starflower pincushions, belongs to the Caprifoliaceae family. It is an endemic North African herbaceous, bristly-hairy annual plant (Pottier-Alapetite, 1981). In folk medicine, leaves and flowers of *Scabiosa stellata* were used in Morocco to treat heel cracks (Bammi and Douira, 2002). The majority of *Scabiosa*, comprising about 100 species, occurs in the Mediterranean region (Carlson et al., 2012) and among them, approximately 12 species can be found in Algeria (Quezel and Santa, 1963). Up to date, chemical investigations of *Scabiosa* species have mainly revealed the presence of saponins (Alimbaeva et al., 1977; Baykal et al., 1998; Zheng et al., 2004), flavonoids, coumarins (Garaev et al., 2008), and iridoid glucosides (Papalexandrou et al., 2003; Polat et al., 2010). The aglycones of *Scabiosa* saponins were identified as oleanolic acid, hederagenin, and ursolic acid with glucose, rhamnose, xylose, and arabinose as sugar (Akimaliev et al., 1976a,b, Yusifova and Movsumov, 2015; Zheng et al., 2004), or pomolic acid with glycoside containing an allose in *Scabiosa rotata* saponins (Baykal et al., 1997, 1998). Previous chemical studies of *S. stellata* demonstrated the presence of fatty acids, β-sitosterol, stigmasterol, oleanolic, ursolic acids, bis-iridoids and flavonoids (Lehbili et al., 2018; Rahmouni et al., 2017). In a continuing of our search for bioactive constituents from Algerian flora, *Scabiosa stellata* L. was phytochemically investigated, and eight undescribed triterpenoid saponins, namely, scabiostellatosides A-H (**1**–**8**), together with three known compounds (**9**–**11**) were isolated (Fig. 1). Herein, we report the isolation and structural elucidation of the undescribed triterpenoid saponins, along with the evaluation of their cytotoxic activity against human fibrosarcoma HT1080 cell line.

2. Results and discussion

The 70% EtOH extract from the whole plant of *S. stellata* was subjected to Diaion HP-20 resin chromatography to give the saponin-containing fractions, which were subjected to further column chromatography to yield eight undescribed triterpenoid

* Corresponding author.
E-mail address: abdulmagid.alabdulmagid@univ-reims.fr (A. Alabdul Magid).

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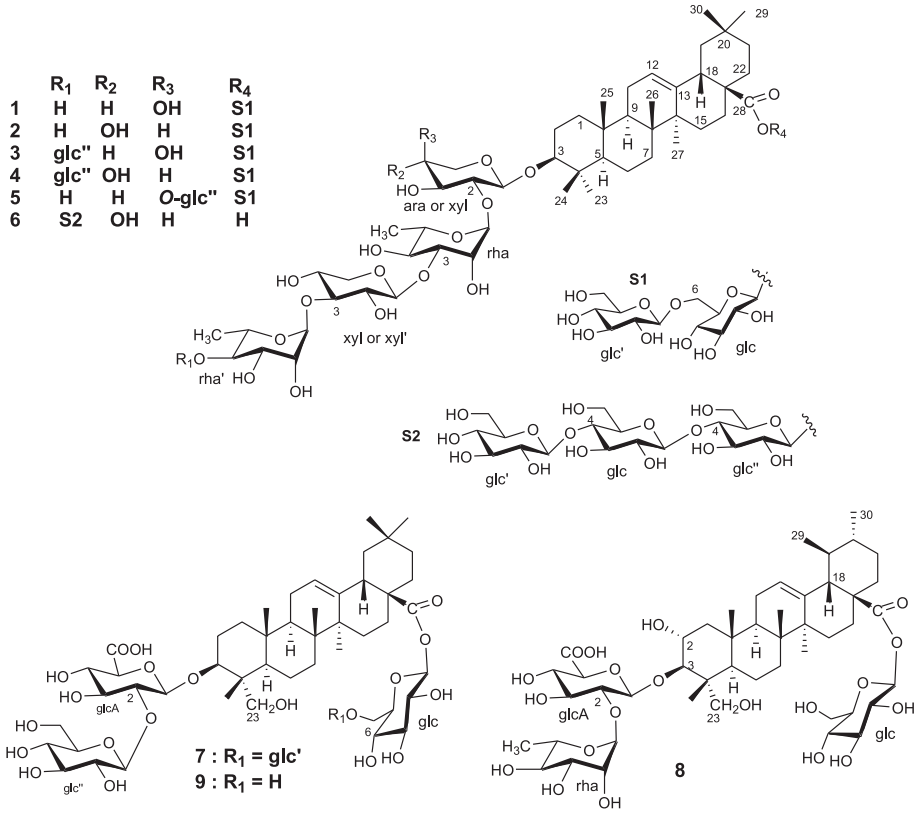

Fig. 1. The structures of compounds **1**–**9** isolated from *Scabiosa stellata*.

saponins (**1**–**8**) and three known compounds (**9**–**11**) (Fig. 1). Their structures were established by spectroscopic data analyses (1D, 2D-NMR and HRESIMS) and by comparison with literature data. Acid hydrolysis of an aliquot of the saponin-containing fraction allowed the identification of five monosaccharides as D-glucose, D-xylose, D-glucuronic acid, L-arabinose and L-rhamnose by comparison with authentic samples (see Experimental Section).

Scabiostellatoside A (**1**) was obtained as amorphous white powder. Its molecular formula, $C_{64}H_{104}O_{29}$, was determined by the positive-ion HRESIMS at *m/z* 1359.6552 $[M + Na]^+$ (calcd for 1359.6561). The ^{1}H NMR spectrum displayed characteristic resonances of an olean-12-ene skeleton, namely, seven tertiary methyls at δ_H 0.83, 0.88, 0.93, 0.97, 0.99, 1.05 and 1.18, an oxymethine at δ_H 3.15 (dd, $J = 11.6, 4.2$ Hz), and an olefinic proton resonance at δ_H 5.27 (t, $J = 3.4$ Hz). The ^{13}C NMR spectrum showed resonances for one carboxyl group (δ_C 176.7), two olefinic carbons (δ_C 122.4, 143.5), one downfield glycosylation shifted oxygenated methine (δ_C 89.2), and seven methyls. Taken together, these data were indicative of a typical oleanolic acid (Alabdul Magid et al., 2015). This assumption was confirmed by analysis of the COSY, TOCSY, ROESY, HSQC and HMBC spectra which allowed the full assignment of the proton and carbon resonances of the aglycone (Table 1). In the ROESY spectrum, correlations observed between H-3/H-5 and H-5/H-9 indicated their α-axial orientation and thus the β-orientation of the oxygen at C-3. The sugar part of **1** consists of six residues as evidenced by ^{1}H NMR spectrum which displayed six anomeric protons at δ_H 4.36, 4.49, 4.51, 5.19, 5.20 and 5.37, showing correlations in the HSQC spectrum to carbons at δ_C 103.3, 105.1, 103.9, 101.1, 100.1 and 94.4, respectively (Table 2). Two α-L-rhamnopyranose units (rha and rha') were identified by equatorial anomeric protons [δ_H 5.20 (d, $J = 1.5$ Hz, rha); 5.19 (d, $J = 1.4$ Hz, rha')], the small coupling constant between $H_{eq\text{-}2}$ and $H_{ax\text{-}3}$ ($J = 3.5$ Hz), the large coupling constants between $H_{ax\text{-}3}$ and $H_{ax\text{-}4}$ ($J > 9.5$ Hz), and the coupling constant values of 6.2 Hz of methyl doublets [δ_H 1.24 (rha); 1.27 (rha')] (Table 2) (Chang et al., 2007). The NMR signals belonging to two β-D-glucopyranose units were assigned starting from the anomeric proton at δ_H 5.37 (d, $J = 8.1$ Hz, glc') and 4.36 (d, $J = 7.8$ Hz, glc). The H-1, H-2, H-3 and H-4 of glc and glc' exhibited large vicinal couplings (≥7.8 Hz) indicating that all protons are axial (Table 2). The fifth sugar unit was identified as α-L-arabinopyranose [$\delta_{H\text{-}1}$ 4.51 (d, $J = 5.3$ Hz, ara)] based on the large $J_{H\text{-}1,H\text{-}2}$ and $J_{H\text{-}2,H\text{-}3}$ (7.1 Hz) and the small couplings $J_{H\text{-}3,H\text{-}4}$ (3.4 Hz) indicating that the H-4 was equatorial (Table 2) (Alabdul Magid et al., 2015; Zheng et al., 2004). The last monosaccharide unit was identified as a β-D-xylopyranose moiety [$\delta_{H\text{-}1}$ 4.49 (d, $J = 7.6$ Hz, xyl)] by interpretation of 2D-NMR spectra. The H-1, H-2, H-3 and H-4 of xyl exhibited large vicinal couplings (≥7.6 Hz) indicating that all are axials (Table 2). The ^{1}H and ^{13}C NMR spectra of **1** displayed many similarities with those of scabiosaponin A (3-*O*-[β-D-glucopyranosyl-(1 → 4)-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranonosyl]-28-*O*-[β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl]-oleanolic acid) (Zheng et al., 2004), the difference was the nature and the position of attachment of last sugar residue linked to the xylose, α-L-rhamnopyranose in **1** instead of β-D-glucopyranose in scabiosaponin A. The cross-peak observed in the HMBC spectrum between glc'-H-1/glc-C-6 (δ_C 68.1) and glc-H-1/aglycone-C-28 (δ_C 176.7) established the disaccharide [glc'-(1 → 6)-glc] to be linked to the C-28 of the aglycone. In a similar fashion, the HMBC correlation between rha'-H-1/xyl-C-3 (δ_C 82.1), xyl-H-1/rha-C-3 (δ_C 80.6), rha-H-1/ara-C-2 (δ_C 75.0) and ara-H-1/aglycone-C-3 (δ_C 89.2) indicated that the tetrasaccharide [rha'-(1 → 3)-xyl-(1 → 3)-rha-(1 → 2)-ara] was attached to the C-3 of the aglycone (Fig. 2). In addition, ROESY correlations confirming the interglycosidic linkage and the point of attachment of the tetra-saccharide at the C-3 of the aglycone were

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