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Original article

Iridoid and Furanolabdane -Type Diterpene Glycosides from Rhizomes of *Eremostachys azerbaijanica* Rech. f.

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Abstract

Background and objectives: The rhizomes of *Eremostachys azerbaijanica* Rech. f., as an indigenous plant in East Azerbaijan province of Iran, were studied for isolation and identification of possible phytoconstituents. **Methods:** The air- dried and ground rhizomes were extracted with n-hexane, dichloromethane (DCM) and methanol (MeOH) using a Soxhlet apparatus. The 10%, 20% and 80% MeOH in water C18 cartridge solid phase extraction products (Sep-Pak fractions) of the MeOH extract were subjected to preparative reversed- phase high performance liquid chromatography (RP-HPLC) and the isolated pure compounds were identified by one- dimensional nuclear magnetic resonance (1D-NMR) spectroscopic technique. **Results:** The spectroscopic data of the compounds were compared with the respective published data and the obtained results showed the presence of four pure components, 6 - Hydroxy loganin (1), Shanzhiside methyl ester (2), Eremostachiin (β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl ester of phlomisoic acid) (3) and Phlomisoside II (4), with iridoid and furano labdane- type diterpene glycoside structures. **Conclusion:** The occurrence of these types of chemical structures might be a confirmation to close relation and similar pharmacological and biological activities between *Eremostachys* and *Phlomis* genera.

Keywords: *Eremostachys azerbaijanica*; furanolabdane diterpene; iridoid; Lamiaceae

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Introduction

Desert rod or *Eremostachys* from Lamiaceae family, is a genus with 60 known species distributed mainly in the Middle-East, central and western Asia. The genus contains 15 species of perennial herbs in Iran [1-4]. According to previous investigations, some species are traditionally used for a variety of ailments. For example, *Eremostachys laciniata* (L.) Bunge has been used orally as a remedy for allergies, headache and liver disorders [5]. Further studies have indicated various effects such as local analgesic, anti-inflammatory, anti-nociceptive, anti-bacterial, anti-depressant and anti-oxidant properties [5-9]. It has also been effective in treatment of mild and moderate Carpal Tunnel Syndrome (CTS) [10].

Eremostachys macrophylla Montbr.& Auch. is another species in Iran that is used in folk medicine for treatment of wound healing, snake bites, rheumatism and joint pains [11]. Likewise, our previous findings suggested antimalarial and cytotoxic effects from the aerial parts and rhizomes of this species [11-14]. Unpublished indigenous knowledge has shown local analgesic and anti-inflammatory effect from the rhizomes of *Eremostachys glabra* Boiss [15].

Phytochemical studies on just a few species of *Eremostachys* genus have revealed the isolation of different natural compounds in various parts. For example, the rhizomes of *E. laciniata* have been identified as a rich source of phytosterols (stigmasterol, β-sistosterol), phenylethanoids

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(forsythoside B, verbascoside) , flavonoids (luteolin, apigenin, 5,8-dihydroxy-6,7-dimethoxyflavone, 5,7-dihydroxy-6,8-dimethoxyflavone, luteolin 7-*O*-β-glucoside) and iridoid glycosides (9- *epi*-phlomiol, 9-*epi*-pulchelloside II, 6-β-hydroxy-7-*epi*-loganin, lamalbide, sesamoside, 6'-*O*-β-d-glucopyranosyl sesamoside, shanzhiside methyl ester, 5, 9-*epi*-phlomiol, phloyoside II, 5,9-*epi*-penstemoside, 6,9-*epi*-8-*O*-acetyl-shanzhiside metyl ester) [1]. According to Calis et al., thirteen iridoid glycosides, four phenylehanoid structures and six flavonoid derivatives were isolated from the aerial parts of *E. laciniata* [16]. Furanolabdane diterpene glycoside (phlomisoside II and eremostachiin), iridoid glycosides (6, 9-*epi*-8-*O*-acetylshanziside methyl ester, 5,9-*epi*-penstemoside and 5,9-*epi*-7,8-didehydropenstemoside) and ferulic acid derivatives (hexacosyl-(*E*)-ferulate and leucosceptoside A) have been isolated from the rhizomes of *E. glabra* [15,17,18]. Some flavonoid structures (loasifolin, luteolin 4′-*O*-β-d-glucopyranoside, apuleisin, apuleidin, loasins A and B), iridoid glycosides (eremosides A to C, buddlejoside B, 10-O-benzoylcatalpol, pakiside A) and 6,7-dihydroxycoumarin have been isolated from *E. loasifolia* Benth. [19,20]. Moreover, iridoid glycosides (lamalbidic acid, 5-deoxysesamoside, 6β-hydroxy-7-epiloganin, Lamalbide, shanzhiside methyl ester, sesamoside, 5-deoxypulchelloside I) from *E. moluccelloides* Bunge aerial parts and flavonoids (vicarin, soforanarin B, luteolin 7-*O*-β-d-glucopyranoside and hamighriprasin) from *E. vicaryi* Benth have been found [21,22]. Phytochemical evaluations on *E. azerbaijanica* rhizomes and aerial parts have shown the presence of iridoid glicosides (lamalbide, pulchelloside I and sesamoside), phenylethanoid glycosides (forsythoside B, acetoside and alyssonoside) and flavonoid derivatives (luteolin-7-O-rutinoside) [23-25]. In this study MeOH extract of *E. azerbaijanica* rhizomes as an indigenous species growing in East Azarbaijan province, Iran, was subjected to more phytochemical investigation and identification of other natural components.

Material and Methods

Plant material

Rhizomes of *E. azerbaijanica* Rech.f. were collected during flowering stage from Bostan abad, Eastern Azerbaijan (37° 51' N, 46° 51' E), Iran, in July 2012. The identity of the plant was confirmed by anatomical examination in comparison with the herbarium specimens (voucher Nos. TBZ-fph-738) deposited in the Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Extraction, isolation and identification of compounds

The air-dried and ground rhizomes of *E. azerbaijanica* (50 g) were extracted with n-hexane, dichloromethane (DCM) and MeOH (Caledon, Canada), successively with a Soxhlet apparatus (500 mL each).

The MeOH extract (2 g) was subjected to solid phase extraction (SPE) using a C_{18} Sep-Pak cartridge (Waters, USA) , eluting with a step gradient of MeOH/water mixture (10:90, 20:80, 40:60, 60:40, 80:20 and 100:0). All extracts and fractions were separately concentrated using a rotary evaporator at a maximum temperature of 45 °C. The 10%, 20% and 80% MeOH in water Sep-Pak fractions were also subjected to preparative reversed-phase HPLC (prep-HPLC) conducted on a Knauer HPLC (preparative pump 1800) fitted with a C_{18} column (250 mm length, 20 mm i.d, 10 µm particle size, Dr. Maisch, Germany) system. The mobile phase consisting of 0%-40% MeOH in water for 10% MeOH fraction, 20%-40% MeOH in water for 20% MeOH fraction and 67%-90% MeOH in water for 80% MeOH fraction at flow rate of 8 ml/min, in 75 min run time and a detector set at 220 nm was used. The isolated pure compounds were identified by a Bruker Spectrospin 400 MHz NMR-spectrometer, Germany. The spectroscopic data of the known compounds were compared with the respective published data [1].

Results and Discussion

The solid phase extraction of the MeOH extract from *E. azerbaijanica* rhizomes followed by reversed-phase preparative HPLC analysis of the 10%, 20% and 80% fractions of MeOH extract led to the identification of two iridoid and two furanolabdane diterpene glycoside structures. These compounds were identified unequivocally, on the basis of ^{1}H-NMR, ^{13}C-NMR and UV spectrum as 6 - Hydroxy loganin (1) (colorless; 12 mg; t_R= 44.81 min; λ_{max} (MeOH)= 237 nm), Shanzhiside methyl ester (2) (yellow; 5 mg; t_R= 13.04 min; λ_{max} (MeOH)= 235 nm) Eremostachiin (3) or β-D-glucopyranosyl-(1→2)-β-D-

glucopyranosyl ester of phlomisoic acid (white needles; 21 mg; t_R= 19.25 min; λ_{max} (MeOH)= 207 nm) and Phlomisoside II (4) (white needles; 6 mg; tR = 22.33 min; λ_{max} (MeOH)= 207 nm). The spectroscopic data of the known compounds from 10% and 20% MeOH fractions have been shown in table 1

Table 1. ^{1}H-NMR spectroscopic data for compounds 1 and 2

Position	Chemical shift δ in ppm (1)		Chemical shift δ in ppm (2)	
	δ H	δ C	δ H	δ C
1	5.39, d (J: 2.93 Hz)	93.63	5.54, bs	93.79
2	-	-	-	-
3	7.35, s	150.21	7.38, s	151.78
4	-	108.37	-	109.77
5	2.69, dd (J: 8.63, 4.06 Hz)	37.54	2.94, bd (J: 8.50 Hz)	38.77
6	3.47, dd (J: 9.06, 5.98 Hz)	80.94	4.08, m	75.51
7	3.66*	82.40	(a): 1.79, dd (J: 13.40, 5.98 Hz) (b): 2.07, dd (J: 13.42, 6.40 Hz)	47.73
8	1.60, m	35.37	-	77.96
9	2.06, m	40.90	2.64, bd (J: 10.19 Hz)	49.56
10	1.03 (3H), d (J: 6.56 Hz)	13.79	1.18 (3H), s	23.24
11	-	168.24	-	169.52
OCH3	3.64(3H), s	50.32	3.67, s	51.84
1'	4.66*	96.96	4.70*	98.18
2'	3.16, t (J: 8.99 Hz)	70.99	3.20, m	72.51
3'	3.22-3.40*	73.98	3.26-3.43*	75.24
4'	3.22-3.40*	67.94	3.26-3.43*	69.49
5'	3.22-3.40*	74.72	3.26-3.43*	76.24
6' (a) 6' (b)	3.63, dd(12.42, 5.8 Hz) 3.82, bd(12.29 Hz)	59.05	3.63, dd(12.0, 5.91 Hz) 3.86, bd (J: 11.83 Hz)	60.61

*Overlapped peaks; spectra obtained in D_2O; 400 MHz

The spectroscopic data of the known compounds from 80% MeOH fraction have been presented in table 2 and also compared with the respective published data.

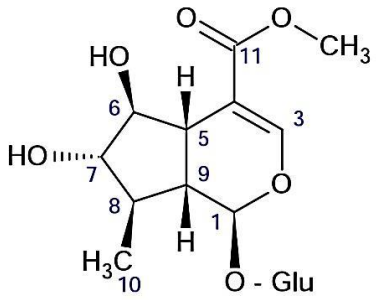
Pursuant to table 1, both of the compounds (1) and (2) showed UV, ^{1}H-NMR and ^{13}CNMR signals in agreement with iridoid glycoside skeletons [26]. In the case of compound (1), the signals presented a methyl group at C_8 (δ_{H10}: 1.03 ppm, δ_{C10}: 13.79 ppm), a methoxy group ($\delta_{H(OCH3)}$: 3.64 ppm, $\delta_{C(OCH3)}$: 50.32 ppm), an olefinic methine at C_3 (δ_{H3}: 7.35 ppm, δ_{C3}: 150.21 ppm), oxymethines at C_1 (δ_{H1}: 5.39 ppm, δ_{C1}: 93.63 ppm) , C_6 (δ_{H6}: 3.47 ppm, δ_{C6}: 80.94 ppm) and C_7 (δ_{H7}: 3.66 ppm, δ_{C7}: 82.40), two methine at C5 (δ_{H5}: 2.69 ppm, δ_{C5}: 37.54 ppm) and C9 (δ_{H9}: 2.06 ppm, δ_{C9}: 40.90 ppm) and a β-glucose unit ($\delta_{H1'}$: 4.66 ppm, $\delta_{C1'}$: 96.96 ppm).

Table 2. ^{1}H-NMR and ^{13}C-NMR spectroscopic data for compounds 3 and 4

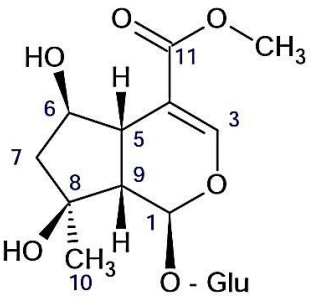
Position	Chemical shift δ in ppm (3)		Chemical shift δ in ppm (4)	
	δ_H	δ_C	δ_H	δ_C
1(a) 1(b)	1.14, m 1.83*	36.71	-* -*	34.62
2(a) 2(b)	2.03, m -*	19.54	-* -*	26.17
3(a) 3(b)	0.99, m 2.19, m	37.14	-* -	88.46
4	-	43.55	-	38.03
5	1.71, m	53.02	-*	50.97
6(a) 6(b)	2.04* -*	20.43	-* -*	21.19
7(a) 7(b)	2.03* -*	33.96	-* -*	33.31
8	-	126.57	-	125.85
9	-	138.87	-	139.54
10	-	38-45*	-	38.73
11 (a) 11(b)	2.19* -*	28.70	-* -*	28.59
12(a) 12(b)	2.37* -	25.35	-* -*	25.32
13	-	125.09	-	125.07
14	7.46, s	138.67	7.47, s	138.68
15	7.53, bs	143.03	7.54, s	142.99
16	6.39, bs	111.05	6.41, s	111.06
17	1.59 (3H), s	19.25	1.56 (3H), s	18.27
18	1.21 (3H), s	28.05	1.02 (3H), s	27.72
19	-	175.54	0.92 (3H), s	16.13
20	0.79 (3H), s	18.24	0.77 (3H), s	19.96
21	-	-	-	-
1'	5.44, d(J:8 Hz)	92.06	4.30, d(J:7Hz)	103.57
2'	3.68*, m	77.71	2.98-3.17*	81.12
3'	3.68*	77.49	3.31-3.50*	76.89
4'	3.41-3.48*	70.16	3.31-3.50*	69.99
5'	3.60*	76.83	3.31-3.50*	76.43
6'(a) 6'(b)	3.60* 3.66*	61.23	3.61-3.68* 3.61-3.68*	61.10
1"	4.58, d(J:7.69 Hz)	102.85	4.15, t	103.79
2"	3.00, m	74.60	2.98-3.17*	75.23
3"	3.41-3.48*	76.35	3.31-3.50*	76.16
4"	3.41-3.48*	69.47	3.31-3.50*	69.93
5"	3.41-3.48*	77.15	3.31-3.50*	76.58
6"(a) 6"(b)	3.59* 3.68*	60.61	3.61-3.68* 3.61-3.68*	60.95

*Overlapped peaks; Spectra obtained in deuterated DMSO; 400 MHz

Moreover, for the ^{1}H-NMR and ^{13}C-NMR data of compounds (2) the signals showed a methyl group at C_8 (δ_{H10}: 1.18 ppm, δ_{C10}: 23.24 ppm), a methoxy group ($\delta_{H(OCH3)}$: 3.67 ppm, $\delta_{C(OCH3)}$: 51.84 ppm), an olefinic methine at C_3 (δ_{H3}: 7.38 ppm, δ_{C3}: 151.78 ppm), oxymethines at C_1 (δ_{H1}: 5.54 ppm, δ_{C1}: 93.79 ppm) , C_6 (δ_{H6}: 4.08 ppm, δ_{C6}: 75.51 ppm), a methylene bridge at C_7 (δ_{H7}: 1.79, 2.07 ppm, δ_{C7}: 47.73), two methine at C5 (δ_{H5}: 2.94 ppm, δ_{C5}: 38.77 ppm) and C9 (δ_{H9}: 2.64 ppm, δ_{C9}: 49.56 ppm) and a β-glucose unit ($\delta_{H1'}$: 4.70 ppm, $\delta_{C1'}$: 98.18 ppm).

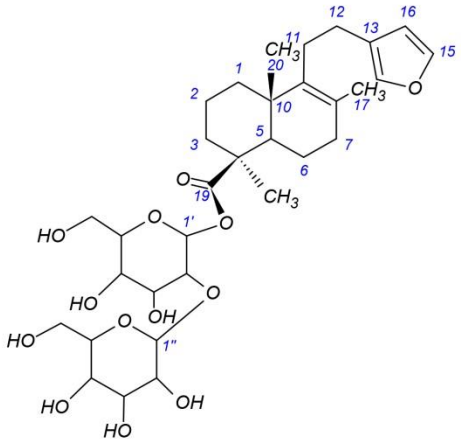


6 - Hydroxy loganin (1)

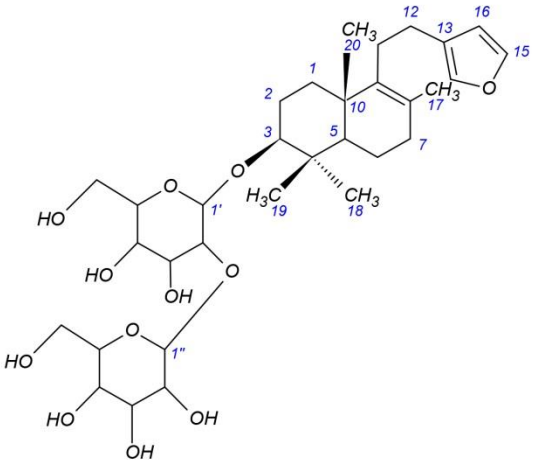


Shanzhiside methyl ester (2)

Figure 1. Two iridoid glycoside structures



Eremostachiin (3)



Phlomisoside II (4)

Figure 2. Two furanolabdane-type diterpenoide glycoside structures

Calis and et al. have reported 6 - hydroxy loganin and shanzhiside methyl ester from the aerial parts of *E. laciniata* and *E. moluccelloides* [16,22].

According to table 2, in the ^{1}H-NMR spectrum of compound (3), there were signals attributable to eremostachiin as a furanolabdane-type diterpenoide glycoside that have been reported previously from *E. glabra* rhizomes [17] with an ethylfuran moiety (δ 2.19, 2.37, 6.39, 7.46 and 7.53 ppm) three methyls (δ 0.79, 1.21 and 1.59 ppm), five methylene (δ 0.99-2.19 ppm), a methine (δ 1.71 ppm) and also two glucose units (δ anomeric protons: 5.44 ppm and 4.58 ppm, others: 3.00-3.68 ppm).

The spectroscopic data of compound (4) were also in agreement with the previous literatures [17,27,28]. The signals showed the presence of a furan part (δ 6.41, 7.47, 7.54 ppm) four methyls (δ 0.77, 0.99, 1.02 and 1.56 ppm) and two glucose units (δ anomeric protons: 4.30 ppm and 4.15 ppm, others: 2.98-3.68 ppm) and these data were in agreement with a known furanolabdane-type diterpenoide glycoside structure, phlomisoside II. These two suggested structures were confirmed by the ^{13}C-NMR spectrum, which indicated characteristic signals such as 11 aliphatic carbons (δ 18-54 ppm), two anomeric carbons (δ 92.06 and 102.85 ppm), carbons of ethylfuran group (δ 25.35, 28.70, 111.05, 125.09, 138.67 and 143.03 ppm), carbonyl group (δ 175.54 ppm) and two vinyl carbons (δ 126.57 and 138.87 ppm) for compound (3).

^{13}C-NMR data of compound (4) exactly referred to phlomisoside II, which showed signals for 11 aliphatic carbons (δ 16-51 ppm), two anomeric carbons (δ 103.57 and 103.79), ethylfuran carbons (δ 28.59, 25.32, 111.06, 125.07, 138.68 and 142.99 ppm) and two vinyl carbons (δ 125.85 and 139.54 ppm).

Regarding previous evaluations, these two furanolabda-type diterpenoide structures had a low antioxidant activity comparing to quercetin [13]; however further research is needed for understanding the biological effects of them.

The presence of iridoid glycosides (e. g. shanzhiside methyl ester, barlerin, sesamoside and penstemoside) and furanolabdane-type diterpenoide glycoside structures (e. g. phlomisosides I-IV) have been reported from the genus *Phlomis* previously. Both the *Eremostachys* and *Phlomis* genera belong to Lamiaceae family. Similar morphology and chemotaxonomic studies on this family using some chemotaxonomic markers such as flavonoids, have shown some points of similarity between these two genera. The existence of iridoids and furanolabdane-type diterpenoides in closely related genera could be important chemotaxonomically and might be a reason for the same biological effects [17,28-31].

Iridoid glycosides as a class of natural structures isolated from different species of plants exhibit a wide range of pharmacological and biological effects. According to previous literatures, they are used in the preparation of anti-inflammatory, anti-rheumatic, anti-ulcer, bitter tonics, febrifuges, cough medicines, sedatives, hypo and hypertensive drug formulations. Other pharmacological and biological effects of these structures are anti-bacterial, anti-fungal, anti-protozoal, anti-viral, anti-oxidative, anti-cancer, anti-coagulant, anti-diabetic, anti-hyperlipidaemic, anti-nociceptive, anti-osteoporosis, human neutrophil elastase inhibitory, immunomodulatory, melanogenesis inhibitory, hepatoprotective, neuroprotective and neuritogenic activities [32-34]. The presence of common phytochemicals in the plants can be a reason for their similar pharmacological and biological effects. It is noteworthy that, this is the first report of the identification of furanolabdane-type diterpenoide glycoside in *E. azerbaijanica*.

Considering the results, the rhizome of *E. azerbaijanica* could be a good source for iridoid and furanolabdane-type diterpenoide glycoside structures, which have been previously reported from the genus *Phlomis* and other species of *Eremostachys* (*E. glabra* and *E. laciniata*) [17, 28-30].

The occurrence of similar structures could be a confirmation to the close relation between *Eremostachys* and *Phlomis* genera and the cause of similar pharmacological and biological activities.

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Author contributions

Abbas Delazar: design and supervision of the study; Sedigheh Bamdad Moghaddam: performing NMR spectroscopy; Solmaz Asnaashari: drafting of the manuscript, data analysis and acquisition of data.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

DCM: dichloromethane; MeOH: methanol; SPE: solid phase extration; HPLC: high performance liquid chromatography; NMR: nuclear magnetic resonance; UV: ultraviolet