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Sedative and antinociceptive activities of two new sesquiterpenes isolated from *Ricinus communis*

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[ABSTRACT] Two new sesquiterpenes, trivially named ricinusoids A (**1**) and ricinusoids B (**2**), were isolated from ethyl acetate fraction of *Ricinus communis*. The structures of new compounds were elucidated by detailed spectroscopic techniques, including 1D- and 2D-NMR, UV, IR spectroscopy, and mass spectrometry. The compounds (**1**−**2**) were also assessed for *in-vivo* sedative and analgesic like effects in open field and acetic acid induced writhing tests respectively at 5, 10, and 20 $mg \cdot kg^{-1}$ i.p. Pretreatment of both test compounds caused significant ($P \leq 0.05$) reduction in locomotive activity like sedative agents and abdominal constrictions like analgesics. Both compounds (**1**−**2**) possessed marked sedative and antinociceptive effects in animal models.

[KEY WORDS] *Ricinus communis*; Sesquiterpenoids; Euphorbiaceae; Spectroscopic techniques; Antinociceptive activity

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Introduction

Ricinus communis, known as castor bean, is a tropical plant of family Euphorbiaceae distributed throughout the world. It grows as annual herb in temperate regions and is also cultivated for ornamental purposes [1-2]. *R. communis* is reported to have anticancer, antidiabetic, and antiprotozoal activities [3]. Similarly, leaf, root and seed oil of *R. communis* have been used by local practitioners for cure of inflammation, hypoglycemic, and liver disorders [3-4]. The ethanolic extract of *R. communis* is reported to have antidiabetic and antiasthmatic activities and is also effective to prevent infections when used in combination with immunosuppressant drugs [5-6]. *R. communis* has been used as insecticidal agent against termites to prevent damage of wood [7]. *R. communis* also possesses antioxidant, anti-inflammatory, free radical scavenging, antifertility, and antitumor activities [8-11].

Various chemical constituents isolated from leaves of *Ricinus communis* are kaemferol-3-*O*-*β*-drutinoside, kaemferol-3-*O*-*β*-d-xylo pyranoid, tannins, gallic acid, and quercetin [12-13]. Phytochemicals like Ricin A, Ricin B, ricinus agglutinin, and indole-3-acetic acid have been isolated from seeds of *Ricinus communis,* while ricinine and diterpenoid hydrocarbons are reported from fruits and seedlings of castor bean [14-18].

The isolated new sesquiterpenoids provisionally called ricinusoids A (**1**) and ricinusoids B (**2**) have been isolated first ever time from genus *Ricinus*. Keeping in view the medicinal importance of *Ricinus communis,* two new sesquiterpenes ricinusoids A (**1**) and ricinusoids B (**2**) were isolated from *Ricinus communis* and investigated for *in vivo* sedative and analgesic activities.

Results

The ethyl acetate fraction of *Ricinus communis* was subjected to column chromatography, which resulted the isolation of two new sesquiterpenoids (**1**−**2**) and structure elucidation were carried out by different spectroscopic techniques, with

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comparison of literature as well.

Compound **1** was isolated as gummy solid and assigned a molecular formula ($C_{16}H_{20}O_3$) on the basis of highest peak at *m/z* 260 $[M]^+$ in HR-EI-MS. The IR spectrum showed absorption bands at 2 960, 1 680, 1 402, and 906 cm^{-1}, indicating the presence of alkenyl group, carbonyl group, and ether moiety, while UV spectrum showed bands at λ_{max} 230 and 290 nm.

The ^1H NMR spectrum (Table 1) of compound **1** revealed the presence of three methyl groups at δ_H 1.40 (3H, s), 1.62 (3H, s), and 1.80 (3H, s) and a methoxy group appeared at δ_H 3.56 (3H, s), while two olefinic protons centered at δ_H 4.92 (2H, s). Similarly, ^1H NMR also revealed the presence of two methylene groups at δ_H 2.14 (2H, s), 2.52 (1H, m), and 2.87 (1H, m) and two methine groups at 6.50 (1H, s) and 2.20 (1H, dd, J = 11.6, 6.1 Hz). The ^{13}C NMR DEPT experiment suggested the presence of sixteen carbon atoms comprising of three methyl groups, one methoxy group, three methylenes, two methines, and seven quaternary carbons (Table 1). The ^{13}C NMR spectrum showed quaternary carbons at δ_C 138.4, 120.3, 40.1, 167.1, and 142.7, while two carbonyl carbons at δ_C 199.6 and 185.4. Three methyl groups centered at δ_C 14.7, 24.4, and 23.1 and a signal for methoxy group at 57.4 were displayed in ^{13}C NMR spectrum (Fig. 1).

The accurate placement of substituent in compound **1** was supported by HMBC (Heteronuclear multiple bond correlation) and COSY (Correlation spectroscopy) experiments. The COSY spectrum showed strong correlations between H-8/H-8a. In HMBC spectrum H-2 (δ_H 6.50) with C-1 (δ_C 199.6) and C-3 (δ_C 167.1), C-9 (δ_C 142.7), C-4 (δ_C 36.9), and C-8a (δ_C 44.7), while H-8 (δ_H 2.52 & 2.87) showed correlation with C-8a (δ_C 44.7) and C-7 (δ_C 185.4), C-6 (δ_C 138.4) and C-1 (δ_C 199.6). Similarly CH_3-12 showed HMBC cross peaks with C-4a (δ_C 40.1), C-4 (δ_C 36.9) and C-5 (δ_C 120.3). Finally, correlations of CH_3-11 with C-9 (δ_C 142.7), C-3 (δ_C 167.1) and C-10 (δ_C 114.7) confirmed the position of alkenyl moiety. In the same way, the placement of side chain alkenyl moiety was further supported by the HMBC correlations of CH_2 (δ_H 4.92) with that of C-9 (δ_C 142.7), C-11 (δ_C 23.1), and C-3 (δ_C 167.1). OCH_3 was positioned at C-6 (δ_C 138.4) as depicted in Fig. 2. Compound **1** had two steriogenic centers and the relative stereochemistry was suggested by Nuclear over Hauser Effect (NOE) experiment. The observed NOE interactions were that of CH_3-12 to H-8a, and hence these groups were disposed *cis* to each other as shown in Fig. 3. On the basis of all these facts and comparison with literature [18] the structure of ricinusoid A was established as **1**.

Ricinusoid B (**2**) was isolated as yellow gummy solid from ethyl acetate fraction of *Ricinus communis*. Compound **2** was quite similar to compound **1**, except for few additional signals in NMR. This was also evident from TLC as there was a slight difference in R_f values. Compound **2** was slightly polar. The molecular formula of compound **2** was suggested to be $C_{17}H_{20}O_4$ by HR-EI-MS at *m/z* 288 $[M]^+$ (calculated for $C_{17}H_{20}O_4$. Mass was quite informative in the structure determination of compound **2**, because there was an extra fragment of *m/z* 28 to compound **1**. The UV spectrum showed bands at λ_{max} 218 and 284 nm while IR spectrum showed the presence of alkenyl group, ester moiety and carbonyl group from the absorption bands at 2 940, 1 685, 1 412, 898 cm^{-1} respectively.

Table 1 ^1H NMR and ^{13}C NMR (500 MHz) of compounds 1 and 2 in $CDCl_3$ (J in Hz)

Carbon No.	Compound **1**		Compound **2**	
	δ_H	δ_C	δ_H	δ_C
1	–	199.6	–	197.6
2	6.50 (1H, s)	141.7	6.60 (1H, s)	140.1
3	–	167.1	–	162.6
4	2.14 (2H, s)	36.9	2.20 (2H, s)	35.1
4a	–	40.1	–	39.1
5	–	120.3	–	130.6
6	–	138.4	–	146.8
7	–	185.4	–	187.6
8	2.52 (1H, m) 2.87 (1H, m)	38.7	2.60 (1H, m) 3.01 (1H, m)	41.2
8a	2.20 (1H, dd, J = 11.6, 6.1)	44.7	2.30 (1H, dd, J = 12.7, 5.6)	45.2
9	–	142.7	–	144.1
10	4.92 (2H, s)	114.7	4.86 (2H, s)	112.1
11	1.80 (3H, s)	23.1	2.01 (3H, s)	21.6
12	1.40 (3H, s)	24.4	1.46 (3H, s)	26.1
13	1.62 (3H, s)	14.7	1.70 (3H, s)	16.1
14	3.56 (3H, s)	57.4	–	172.6
15	–	–	2.22 (3H, s)	24.6

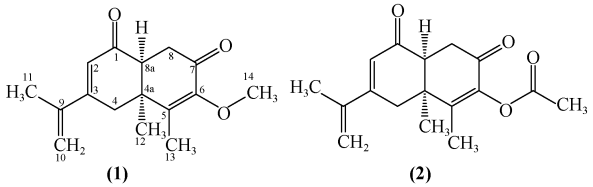

Fig. 1 Structures of compounds 1 and 2

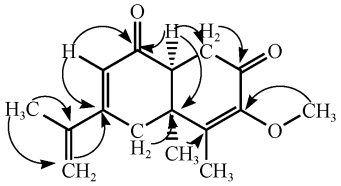

Fig. 2 Important HMBC (H→C) correlations of compound 1

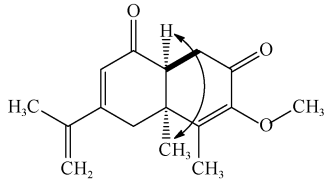

Fig. 3 NOE (◀▶) interactions and COSY (H-H) correlations of compound 1

The ^{1}H NMR and ^{13}C NMR data were quite similar to that of compound **1,** the only difference found was presence of ester moiety at position 6 having chemical shift value of δ_H 2.22 (3H, s) and δ_C 24.6 for methyl group and δ_C 172.6 for quaternary carbon (Table 1). In down field region the chemical shift value for methyl group directly attached to carbonyl group centered at δ_H 2.22 (3H, s), and ^{1}H NMR also confirm the presence of three other methyls. These CH_3 groups showed their chemical shift at δ_H 2.01 (3H, s), δ_H 1.46 (3H, s), and δ_H 1.70 (3H, s). Likewise the other proton signals were in close agreement to those of compound **1**.

The ^{13}C NMR signals of compound **2** were also similar to those of compound **1**, except the signals at δ_C 24.6 and δ_C 172.6 for methyl and carbonyl group.

The COSY and HMBC correlations were quite useful for the proper assignment of substituent in compound **2**. On the basis of above evidences and comparison with literature [18] the structure of ricinusoid B was established as **2** which was unprecedented .

*Characterization of compound **1***

Gummy solid: UV (MeOH) λ_{max}: 230, 290 nm. IR (KBr) υ_{max}: 2 960, 1 680, 1 402, and 906 cm^{-1}. EI-MS *m/z* 260 $[M]^+$ (100), 228.1 (53), 245.1 (71), 230.1 (64), 232.1 (51), 218.1 (35). (HR-EI-MS: *m/z* $[M]^+$ calculated for $C_{16}H_{20}O_3$ 260.141 2, observed 260.142 0). $[\alpha]_D^{25}$ +31 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.50 (1H, s), 2.14 (2H, s), 2.52 (1H, m), 2.87 (1H, m), 2.20 (1H, dd, *J* = 11.6, 6.1 Hz), 4.92 (2H, s), 1.80 (3H, s), 1.40 (3H, s), 1.62 (3H, s), 3.56 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 199.6 (C-1), 141.7 (C-2), 167.1 (C-3), 36.9 (C-4), 40.1 (C-4a), 120.3 (C-5), 138.4 (C-6), 185.4 (C-7), 38.7 (C-8), 44.7 (C-8a), 142.7 (C-9), 114.7 (C-10), 23.1 (C-11), 24.4 (C-12), 14.7 (C-13), 57.4 (C-14).

*Characterization of compound **2***

Yellow gummy solid: UV λ_{max}: 218, 284 nm. IR υ_{max} (KBr): 2 940, 1 685, 1 412, 898 cm^{-1}. EI-MS *m/z* (%): 288 $[M]^+$ (100), 246.0 (57), 245.1 (73), 260.1 (67), 232.1 (39). (HR-EI-MS: *m/z* $[M]^+$ calculated for $C_{17}H_{20}O_4$ for 288.136 2, observed 288.137 1). $[\alpha]_D^{25}$ +43.3 (*c* = 3.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.60 (1H, s), 2.20 (2H, s), 2.60 (1H, m), 3.01 (1H, m), 2.30 (1H, dd, *J* = 12.7, 5.6 Hz), 4.86 (2H, s), 2.01 (3H, s), 1.46 (3H, s), 1.70 (3H, s), 2.22 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.6 (C-1), 140.1 (C-2), 162.6 (C-3), 35.1 (C-4), 39.1 (C-4a), 130.6 (C-5), 146.8 (C-6), 187.6 (C-7), 41.2 (C-8), 45.2 (C-8a), 144.1 (C-9), 112.1 (C-10), 21.6 (C-11), 26.1 (C-12), 16.1 (C-13), 172.6 (C-14), 24.6 (C-15).

Effect in open field test

The results of newly isolated compounds (**1**–**2**) in open field test are presented in Fig. 4. The pretreatment of compounds at all the test doses caused significant decrease in locomotive activity of mice. The overall effects were dose-dependent and the standard compound, bromazepam, was most dominant with absolute immobility of the test mice.

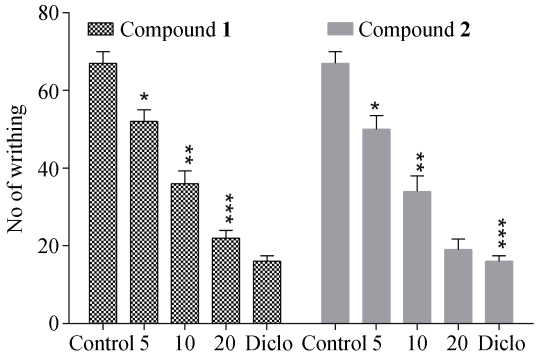

Fig. 4 Effects of intraperitoneal administration of Compounds 1 and 2 in acetic acid induced test. Values are expressed as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* control (*n* = 6). Diclo: Diclofenac sodium

Effects in acetic acid induced writhing test

The anti-nociceptive effects of both isolated compounds (**1**–**2**) in mice are shown in Fig. 5. Both the tested compounds elicited marked attenuation of acetic acid induced writhing. The pain relieving effect was observed in dose-dependent manner while the standard compound, diclofenac sodium was most effective.

Effect of compounds (1 and 2) on acute toxicity

During the 24-h assessment time, compounds **1** and **2** were safe up to the dose of 500 mg·kg^{-1}. Neither gross behavior changes nor mortality was observed.

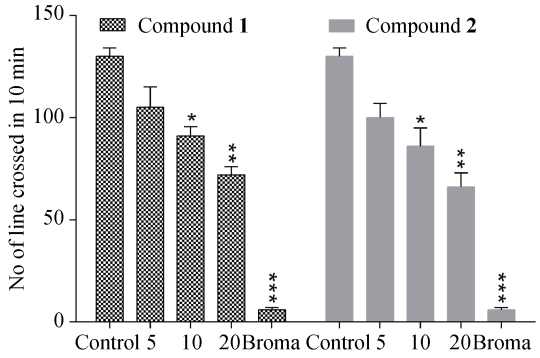

Fig. 5 Sedative activity of compounds 1 and 2. Values are expressed as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* control ($n = 6$). Broma: Bromazepam

Materials and Methods

Extraction and isolation

The whole plant materials (7.5 kg) were collected from District Haripur, KPK Pakistan in September 2014, and identified and authenticated by Dr. Manzoor Ahmed at Department of Botany, Postgraduate College, Abbottabad. A voucher No. 3570 has already been deposited in the herbarium. The materials were shade dried, grinded into fine powder, and extracted with methanol (50 Liters) thrice. The extract was evaporated on vacuum rotary evaporator to get crude extract (350 g). This methanol extract was partitioned into three fractions as *n*-hexane (85 g), ethyl acetate (66 g), and *n*-butanol (93 g).

Ethyl acetate fraction was chromatographed on silica gel eluting with *n*-hexane−EtOAc (100 : 0 to 0 : 100) followed by methanol. 10 sub fractions were collected and examined by TLC on the silica gel. Sub-fractions 5−8 were re-subjected to column chromatography which resulted the isolation of compound **1** (27.3 mg) at *n*-hexane : EtOAc (70 : 30), while compound **2** (26.2 mg) was purified at *n*-hexane : EtOAc (65 : 35).

General experimental procedure

TLCs were carried out using precoated plates (silica gel 60 F254) and silica gel (70−230 mesh and 230−400 mesh, E-Merck, Germany) were used for column chromatography. Jasco-DIP-360-digital polarimeter and JASCO-320-A spectrophotometers were used to record optical rotation and IR spectra, respectively, while UV spectra were recorded on UV-240. Similarly double focusing Varian MAT-312 spectrometer was used to record EI-MS and HR-EI-MS and 1D-NMR and 2D-NMR spectra were recorded using Bruker AMX-500 spectrometer with tetramethylsilane as an internal standard. Chemical shift (δ) values were reported in parts per million and scalar coupling in Hertz (Hz).

Animals

BALB/c mice were used in all experiments. They were fed with standard laboratory food and water ad libitum. Animals were kept under standard condition of temperature and light. Before the start of experiment, the animals were acclimatized with laboratory conditions. The rulings of the institutes of Laboratory Animal Resources, Commission on Life Sciences, National Research Council were maintained during all the experiments. The experimental protocols were approved by the ethical committee (5/pharm) of the Pharmacy Department, University of Peshawar, Pakistan.

Acute toxicity test

The acute toxicity test was carried out to evaluate any possible toxicity for compounds **1** and **2**. Swiss albino mice ($n = 6$) of either sex were tested by administering different doses in increasing or decreasing the dose, based on animal response [19]. The dosing patron was 60, 80, and 100 mg·kg^{-1} p.o., while the control group received only the normal saline. All the groups were observed for any gross effect (restlessness/seizures or any other related effect) and mortality for 24 h.

Open field test

The apparatus used for the activity was consisted of an area of white wood (150 cm in diameter) enclosed by stainless steel walls and divided in four squares by black lines. The open field was placed inside a light and sound-attenuated room. Animals were acclimatized under red light (40 Watt red bulb) for 60 min before the start of experiment in laboratory. The test compounds were injected with (5, 10, and 20 mg·kg^{-1} i.p.). After 30 min, each of the mice was placed in the center of the box and the numbers of lines crossed by the animals were counted [20].

Acetic acid induced writhing test

BALB/c male mice ($n = 6$) weighing 19−22 g were used for this test. All the animals were withdrawn from food 2 h before the start of experiment and were divided into groups. One group was injected with normal saline (10 mL·kg^{-1}) as control, and other received standard drug diclofenac sodium (2.5, 5 and 10 mg·kg^{-1} i.p.) while the remaining groups were injected with 5, 10 and 20 mg·kg^{-1} i.p. of compounds **1** and **2**, respectively. After 30 min of saline, diclofenac sodium and isolated compound, the animals were treated with 1% acetic acid intraperitoneally. The number of abdominal constrictions (writhes) was counted after 5 min of acetic acid injection for the period of 10 min [21-22].

Statistical analysis

Results are expressed as mean ± SEM. One-way ANOVA was used for comparison test of significant differences among groups followed by Dunnet's multiple comparison post test. A level of significance ($P < 0.05$) was considered for each test.

Discussion

The current study revaled that the new isolated compounds (**1**−**2**) from *Ricinus communis* possessed strong sedative like effect in open field test and anti-nociceptive effect in acetic acid induced writhing test without any toxicity during a 24-h assessment.

The open field test is widely used to measure the locomotive activity of test compounds which determine the sedative like potential [23-25]. Pretreatment of mice with the compounds (**1**−**2**) showed dose-dependent reduction in locomotive activ-

ity in open field test as compared to the controls. The reduction in the frequency and amplitude of motion could be attributed to the sedative effects of these compounds.

The acetic acid induced writhing test is a non-specific test usually employed for the assessment of antinociceptive effect of test articles [26-28]. When our test compounds (**1**−**2**) were challenged against acetic acid induced abdominal constriction test, both caused significant reduction in number of abdominal constriction and thus suggesting analgesic like effect.

The acute toxicity test is commonly used to measure the first safety profile of test compounds in terms of gross behavioral changes and mortality. The results of compounds **1** and **2** showed considerable safety in acute toxicity test and suggested that further studies be needed.

Conclusion

The current study accomplished the isolation of two new sesquiterpenoids namely (4a*S*, 8a*S*)-6-methoxy-4a, 5-dimethyl-3-(prop-1-en-2-yl)-4, 4a, 8, 8a-tetrahydronaphtha ene-1, 7-dione (**1**), and (4a*S*, 8a*S*)-1, 8a-dimethyl-3, 5-dioxo-7-(prop-1-en-2-yl)-3, 4, 4a, 5, 8, 8a-hexahydrona phthalen-2-yl acetate (**2**) from *R. communis*. The structure elucidation and characterization of the compounds were carried out by using mass spectrometry, 1D and 2D-NMR, UV and IR spectroscopy. Both the isolated compounds (**1**−**2**) elicited marked sedative and analgesic like effects in open field and acetic acid induced writhing tests, respectively. Thus, further detailed studies are strongly suggested to establish their clinical prospects.

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