Two New Sesquiterpenoids Isolated From *Cyperus rotundus* L

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Abstract

Two new sesquiterpenoids, isocyperotundone (1) and 1,4-epoxy-4-hydroxy-4,5-seco-guai-11-en-5-one (2), together with 6 known sesquiterpenoids, cyperotundone (3), cyperenoic acid (4), sugetriol triacetate (5), cyperusol A₃ (6), cyperusol A₂ (7), and cyperusol A₁ (8), were isolated from the methanol extract of the rhizomes of *Cyperus rotundus* L. High-resolution electrospray ionization mass spectrometry and 1-dimensional (1D) and 2D nuclear magnetic resonance spectroscopy were used to establish the structures of all the compounds. All the compounds were tested for activity on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. Compounds 1-7 exhibited inhibitory activity on tumor necrosis factor-α-induced activation of the NF-κB pathway, with half-maximal inhibitory concentration values ranging from 34.5 to 73.7 μmol/L.

Keywords

*Cyperus rotundus* L., terpenoids, sesquiterpenoids, bioactivity, NF-κB pathway

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*Cyperus rotundus* L. (Nutgrass, family Cyperaceae) is broadly disseminated in many tropical, subtropical, and temperate regions of the world.¹ The dried rhizomes of *C. rotundus* have been used in traditional medicine to treat various diseases such as spasms, stomach disorders, inflammatory diseases, and women’s diseases in some Asian countries.²–⁶ Phytochemical studies of the species have resulted in the isolation of monoterpenoids, sesquiterpenoids, flavonoids, triterpenoids, and sterols.⁷–¹¹ The plant also possesses a vast array of biological activities, including antipryetic, analgesic, anti-inflammatory, antibacterial, antioxidant, neuroprotective, anticancer, antiinflammatory, and antidiysmenorrhea.¹²–¹⁷ Sesquiterpenoids are the main constituents of this herb with diverse skeletons such as eudesmane, guaiane, patchoulan, cadianane, copeane, and rotundane types.¹⁸–²⁰ As part of our continuing search for new bioactive compounds from medicinal plants, we isolated 2 new sesquiterpenoids, isocyperotundone (1) and 1,4-epoxy-4-hydroxy-4,5-seco-guai-11-en-5-one (2), together with 6 known sesquiterpenoids, cyperotundone (3),²¹ cyperenoic acid (4),²² sugetriol triacetate (5),²³ cyperusol A₃ (6),²⁴ cyperusol A₂ (7),²⁵ and cyperusol A₁ (8)²⁶ from the rhizomes of *C. rotundus*. The structures and molecular formulas of these compounds are shown in Figure 1. The ¹H nuclear magnetic resonance (NMR) and ¹³C NMR spectroscopic data (deuterated chloroform [CDCl₃]) for compounds 3-8 are shown in Supplemental Tables S1-S2. Herein, we report the isolation, purification, and structure elucidation, as well as the inhibitory activity of these compounds against nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling.

Compounds 1 was isolated as a colorless oil. Its molecular formula of C₁₅H₂₂O was determined by high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) from the pseudomolecular ion peak at m/z 219.1743 [M + H]+ (calcd for C₁₅H₂₂OH, 219.1748), with 6 degrees of unsaturation (Supplemental Figure S1). The ¹H-NMR spectrum (Supplemental Figure S2; Table 1) of 1 showed 4 typical methyl groups at δH 1.85 (3H, s, H₂-14), δH 1.27 (3H, s, H₂-12), δH 0.96 (3H, s, H₂-13), and δH 0.73 (3H, d, J = 6.6 Hz, H₂-15); 6 methane protons at δH 2.82 (1H, m, H₃-13), δH 2.67 (1H, dd, 5.7, 11.5 Hz, H₃-6), δH 2.16 (2H, m, H₂-2), δH 1.81 (1H, d, H₁-2), and δH 1.49 (1H, m, H₃-3); and 1 olefin proton at δH 6.18 (1H, s, H-9). The ¹³C-NMR spectrum (Supplemental Figure S3; Table 1), which combines distortionless enhancement by

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polarization transfer (DEPT) (Supplemental Figure S4) and heteronuclear single quantum correlation (HSQC) data (Supplemental Figure S5) for 1, presented 15 carbons including 4 methyl groups (δC 27.9, 25.8, 19.1, 14.7), 3 methylene groups (δC 45.0, 30.9, 27.6), 4 methine groups (δC 128.1, 54.0, 46.8, 31.6), and 4 quaternary carbons (δC 209.4, 141.8, 68.6, 38.8).

The above data suggested that 1 was a patchoulane-type sesquiterpenoid similar to cyperotundone \(^{21,24}\) (3). The main difference between 1 and 3 was that the position of the \(\alpha,\beta\)-unsaturated carbonyl group in 1 changed from C-3/C-4/C-5 to C-8/C-9/C-10. The heteronuclear multiple bond correlation (HMBC) spectrum (Supplemental Figure S6; Table 1) correlations between H3-14 (δH 1.85) and C-10 (δC 141.8), C-9 (δC 128.1) and C-1 (δC 68.6) indicated that the methyl group (Me-14) was attached to C-10, and the correlations from H-9 (δH 6.18) to C-8 (δC 209.4) and C-14 (δC 19.1) with the correlations from H-7 (δH 2.18) to C-8 (δC 209.4) and C-6 (δC 45.0) suggested that the location of the \(\alpha,\beta\)-unsaturated ketone structure was at C-8/C-9/C-10. Other HMBC between H-5 (δH 3.44) to C-1 (δC 68.6) and C-10 (δC 141.8), between H3-14 (δC 1.85) and C-10 (δC 141.8), C-9 (δC 128.1) and C-1 (δC 68.6), between H2-12 (δC 1.27) and C-11 (δC 38.8), C-7 (δC 46.8) and C-1 (δC 68.6), with the correlations from H-7 (δH 2.18) to C-1 (δC 68.6), C-12 (δC 27.9) and C-13 (δC 25.8) indicated the connection of C-1/C-5/C-7/C-11 and proved the existence of a 5-membered ring. Other fragments of 1 were determined from the 1H-1H Correlation Spectroscopy (COSY) spectra (Supplemental Figure S7) correlations of H-2 (δH 2.16)/Ha-3 (δH 1.81), H3-15 (δH 0.73)/H-4 (δH 2.50)/Ha-3 (δH 1.49), and Hb-6 (δH 2.67)/H-7 (δH 2.18). The relative configuration of 1 was elucidated by rotating frame Overhauser effect spectroscopy (ROESY) (Supplemental Figure S8). The key correlation from H-5 (δH 3.44) to H3-15 (δH 0.73) suggested that H-5 and Me-15 were coplanar and assigned a β-orientation. Correlations from H-4 (δH 2.50) to H3-12 (δH 1.27) indicated that H-4 and C-11 were on the same side and defined as α-orientation. Thus, the structure of 1 was determined to be isocyperotundone (Figure 2).

### Table 1. Nuclear Magnetic Resonance Spectroscopic Data (Deuterated Chloroform, 600 and 150 MHz), and Key HMBCs of Compound 1.

| No. | δH (J in Hz) | δC | HMBC        |
|-----|-------------|----|-------------|
| 1   | -           | 68.6|             |
| 2   | 2.16 (2H, m)| 27.6| C-1, C-3, C-4|
| 3   | 1.81 (1H, m)| 30.9| C-1, C-2,   |
| 4   | 1.49 (1H, m)| 31.6| C-1, C-3, C-5, C-15|
| 5   | 2.50 (1H, m)| 54.0| C-1, C-10   |
| 6   | 3.44 (1H, m)| 45.0| C-1, C-10   |
| 7   | 2.82 (1H, m)| 4.0  | C-7, C-8, C-11|
| 8   | 2.67 (1H, m)| 45.0|             |
| 9   | 2.18 (1H, m)| 46.8| C-6, C-13, C-8, C-1 |
| 10  | -           | 141.8|             |
| 11  | -           | 38.8|             |
| 12  | 1.27 (3H, s)| 27.9| C-7, C-7, C-12, C-1 |
| 13  | 0.96 (3H, s)| 25.8| C-7, C-11, C-1 |
| 14  | 1.85 (3H, s)| 19.1| C-9, C-10   |
| 15  | 0.73 (3H, d, 6.6)| 14.7| C-3, C-4 |

Abbreviation: HMBC, heteronuclear multiple bond correlation.
Compound 2 was obtained as a colorless oil. Its molecular formula was assigned as C\textsubscript{15}H\textsubscript{24}O\textsubscript{3} by HR-ESI-MS from the pseudo-molecular ion peak at \(m/z\) 275.1618 [M + Na]+ (calcd for C\textsubscript{15}H\textsubscript{24}O\textsubscript{3}Na, 275.1620), with 4 degrees of unsaturation (Supplemental Figure S10). The infrared (IR) spectrum (Supplemental Figure S21) revealed the presence of a hydroxy group (3429 cm\(^{-1}\)), and due to its strong, wide, and scattered characteristics, there may be intramolecular hydrogen bonds. The \(^1\)H-NMR spectrum (Supplemental Figure S11; Table 2) of 2 showed 3 methyl groups at \(\delta\textsubscript{H} 1.76 (3H, s, H\textsubscript{3}-13), \delta\textsubscript{H} 1.31 (3H, s, H\textsubscript{3}-15), \text{and} \delta\textsubscript{H} 0.90 (3H, d, \textit{J} = 7.1 \text{Hz, H}\textsubscript{3}-14); \) 6 groups of methylene protons at \(\delta\textsubscript{H} 3.50 (1H, m, H\textsubscript{-}6a), \delta\textsubscript{H} 2.21 (1H, m, H\textsubscript{-}6b), \delta\textsubscript{H} 1.98 (1H, m, H-9a), \delta\textsubscript{H} 1.17 (1H, m, H-9b), \delta\textsubscript{H} 2.26 (2H, m, H\textsubscript{2}-2), \delta\textsubscript{H} 1.74 (2H, m, H\textsubscript{2}-3), \text{and} \delta\textsubscript{H} 1.71 (2H, m, H\textsubscript{2}-8) \) and 1 olefinic CH\textsubscript{2} group at \(\delta\textsubscript{H} 4.74 \) (2H, m, H\textsubscript{2}-12). The \(^{13}\)C-NMR spectrum (Supplemental Figure S14; Table 2) in combination with the DEPT experiment (Supplemental Figure S15) allowed the identification of 15 carbons including 3 methyl groups (\(\delta\textsubscript{C} 25.7, 20.3, 15.3\)), 6 methylene groups (\(\delta\textsubscript{C} 109.7, 41.8, 31.0, 30.3, 28.6, 23.0\)), 2 methine groups (\(\delta\textsubscript{C} 44.5, 37.2\)), and 4 quaternary carbons (\(\delta\textsubscript{C} 211.9, 149.0, 99.2, 91.1\)). The NMR spectroscopic data for 2 were quite similar to those of 4,5-seco-guaiane,\textsuperscript{26} which was isolated from Pellia epiphylla, except that the isopropenyl group attached to C-7 replaces the isopropyl group. The HMBCs (Supplemental Figure S17; Table 2) from 2 olefin protons H\textsubscript{2}-12 (\(\delta\textsubscript{H} 4.74\)) and a unimodal methyl group H\textsubscript{3}-13 (\(\delta\textsubscript{H} 1.76\)) to a tertiary carbon C-11 (\(\delta\textsubscript{C} 149.0\)) indicated the presence of an isopropenyl group. This group, which is positioned at C-7, was determined by HMBCs of H\textsubscript{2}-12 (\(\delta\textsubscript{H} 4.74\)) and H\textsubscript{3}-13 (\(\delta\textsubscript{H} 1.76\)) with C-7 (\(\delta\textsubscript{C} 44.5\)). Other fragments of 2 were determined from the \(^1\)H-\(^1\)H COSY spectrum (Supplemental Figure S18) correlations of H\textsubscript{-}2 (\(\delta\textsubscript{H} 2.26\))/H\textsubscript{-}3 (\(\delta\textsubscript{H} 1.74\)) and H\textsubscript{-}6 (\(\delta\textsubscript{H} 3.50\))/H\textsubscript{-}7 (\(\delta\textsubscript{H} 2.32\))/H\textsubscript{-}8 (\(\delta\textsubscript{H} 1.71\))/H\textsubscript{-}9 (\(\delta\textsubscript{H} 1.98\)).

The stereochemical structure of 2 was derived from the ROESY spectrum (Supplemental Figure S19). C-4 of compound 2 was a hemiacetal, indicating the existence of an equilibrium mixture. When the hydroxy group at C-4 has a \(\beta\)-orientation, it could form a stable intramolecular hydrogen bond linked to the ketone at C-5\textsuperscript{26}, therefore it was determined as the dominant configuration. In the ROESY spectrum, major cross-peaks from H\textsubscript{3}-14 (\(\delta\textsubscript{H} 0.90\)) to H\textsubscript{3}-15 (\(\delta\textsubscript{H} 1.31\)) were observed, and the H atoms distance of H\textsubscript{3}-14 and H\textsubscript{3}-15 was 2.7 \times 10^{-10} m (Figure 3), indicating that Me-14 and Me-15 were on the same side and thus had an \(\alpha\)-orientation. The stereochemical structure of C-1 was derived from the ROESY spectrum. Correlations existed between H-10 (\(\delta\textsubscript{H} 1.79\)) and the 2 methylene protons (\(\delta\textsubscript{H} 2.26\)) of C-2 indicated that H-10 and C-2 were on the same side and thus had a \(\beta\)-orientation. Correlations from H-7 (\(\delta\textsubscript{H} 2.32\)) to H-10 (\(\delta\textsubscript{H} 1.79\)) suggested that H-7 and H-10 were on the same side and assigned as \(\beta\)-orientation. In summary, the structure of 2 was determined as 1,4-epoxy-4-hydroxy-4,5-seco-guaian-11-en-5-one (Figure 3).

Figure 2. Key heteronuclear multiple bond correlation (H→C), \(^1\)H-\(^1\)H correlation spectroscopy (H→H), and rotating frame Overhauser effect spectroscopy (H→\(\uparrow\)H) correlations of compound 1.

Table 2. Nuclear Magnetic Resonance Spectroscopic Data (Deuterated Chloroform, 600 and 150 MHz), and Key HMBCs of Compound 2.

| No. | \(\delta\textsubscript{H} (\text{in Hz})\) | \(\delta\textsubscript{C}\) | HMBC |
|-----|---------------------------------|----------------|------|
| 1   | -                               | 91.1           |      |
| 2   | 2.26 (2H, m)                    | 23.0           | C-1, C-4, C-5 |
| 3   | 1.74 (2H, m)                    | 30.3           |      |
| 4   | -                               | 99.2           |      |
| 5   | -                               | 211.9          |      |
| 6   | 3.50 (1H, m)                    | 41.8           | C-5, C-7, C-8, |
| 7   | 2.21 (1H, m)                    | 44.5           | C-6, C-11, C-13 |
| 8   | 2.32 (1H, m)                    | 28.6           | C-6, C-7, C-9 |
| 9   | 1.71 (2H, m)                    | 31.0           | C-7, C-10 |
| 10  | 1.17 (1H, m)                    | 37.2           | C-5 |
| 11  | -                               | 149.0          |      |
| 12  | 1.76 (3H, s)                    | 109.7          | C-7, C-11, C-13 |
| 13  | 1.76 (3H, d, 7.1)               | 20.3           | C-7, C-11, C-12 |
| 14  | 0.90 (3H, d)                    | 15.3           | C-1, C-9, C-10 |
| 15  | 1.31 (3H, s)                    | 25.7           | C-3, C-4 |
| -OH | 3.18 (1H, s)                    | -              | C-4, C-15 |

Abbreviation: HMBC, heteronuclear multiple bond correlation.
The NF-κB transcription factor plays a significant role in regulating various aspects of immune functions, and its abnormal activation is involved in the pathogenesis of diverse autoimmune and inflammatory diseases. The effects of compounds 1-8 on the NF-κB signaling pathway were investigated by the dual-luciferase reporter assay. The results showed that compounds 1-7 can inhibit tumor necrosis factor-alpha (TNF-α)-induced NF-κB activation; half-maximal inhibitory concentration (IC50) values are shown in Table 3.

**Conclusion**

In summary, 8 sesquiterpenoids were isolated and characterized from *C. rotundus* L, including 2 new ones (1 and 2) and 6 known ones (3-8). Compounds 1-7 showed inhibitory effects on the NF-κB signaling pathway, with IC50 values ranging from 34.5 to 73.7 μmol·L⁻¹. Sesquiterpenoids are the main constituents of *C. rotundus*, and they also showed potential biological activities for this herb. As one part of our research on anti-inflammatory components from *C. rotundus*, the study of the new anti-inflammatory sesquiterpenoids provided an efficacious material basis for our follow-up research on biological sesquiterpenoids.

**Experimental**

**Plant Material**

The rhizomes of *C. rotundus* L. were purchased from Shengru Biological Technology Co. Ltd. (batch number: 121059-200706), Yunnan province, China, in January 2018, and authenticated by Associate Professor Xiaoli Liu of Yunnan University of Chinese Medicine.

**General Procedures**

One and 2-dimensional NMR experiments were recorded on a Bruker DRX-600 spectrometer operating at 600 MHz (1H) and 150 MHz (13C) at 300 K (chemical shifts in ppm, coupling constants in Hz) (Bruker, Germany). HR-ESI-MS data were obtained on a Waters AutoSpec Premier P776 mass spectrometer (Waters Co., Milford, MA, USA). High-performance liquid chromatography (HPLC) separation was performed on an Agilent 1260 series with Agilent ZORBAX SB (9.4 × 250 mm) (Agilent Technologies, CA, USA) and YMC-Pack Pro (10 × 250 mm) analytical columns packed with C18 (5 µm) (YMC Co. Ltd., Kyoto, Japan). IR spectra were obtained on a JASCO FT/IR-4600 plus Fourier transform infrared spectrometer using potassium bromide pellets. Column chromatography (CC) was performed on Sephadex LH-20 (GE Healthcare, USA) and silica gel (100, 200, 200-300, or 300-400 mesh) (Qingdao Marine Chemical Inc., Qingdao, China). All solvents used for chromatographic separations were distilled before use. Double luciferase reporter gene detection kits (Promega, United States), Lipofectamine 2000 (Thermo Fisher, USA), Dulbecco’s modified Eagle’s medium, fetal bovine serum, glutamine (Biological Industries, Israel), and dexamethasone (Aladdin, China) were used for the bioassay of compounds.

**Extraction and Isolation**

Powdered and air-dried rhizomes of *C. rotundus* (20 kg) were extracted 5 times with 95% methanol (MeOH) by maceration for 24 hours at room temperature. The MeOH extracts (2 kg) were combined and concentrating under reduced pressure. A portion of this extract was suspended in water (H2O) and...
successively extracted with light petroleum (PE), ethyl acetate (EtOAc), and n-butanol (n-BuOH) to give PE (412 g), EtOAc (200 g), and n-BuOH (98.3 g) fractions, respectively. The PE extract (412 g) was fractionated by CC (2500 g) on silica gel (100, 200 mesh, 15 × 100 cm) eluting with PE/EtOAc (100:0 to 100:100, v/v) to afford 8 fractions (A-H).

Fr. C (27.2 g) was separated using a Sephadex LH-20 column (MeOH) to yield 5 fractions (C-1-C-5). Fr. C-2 (4.9 g) was further separated using silica gel CC (200-300 mesh) and then separated by iterative semi-preparative HPLC to obtain compound 4 (31.7 mg, CH$_2$CN-H$_2$O 80:20, $\nu$ = 1.0 mL/min, $t_R$ = 25.3 minutes). Fr. C-4 (6.7 g) was subjected to silica gel CC (200, 300 mesh) eluting with PE/EtOAc (50:1 to 5:1, v/v) to give yield compound 5 (502.4 mg) after recrystallization, and then purification using a Sephadex LH-20 column (MeOH) afforded compound (11.2 mg) and (6.7 mg).

Fr. D (67.3 g) was separated and subjected to reiterative silica gel CC (200-300, 300-400 mesh) to give compounds 2 (4.5 mg), 7 (3.9 mg), and 8 (3.2 mg). Fr. E (70.3 g) was separated by silica gel CC with PE/EtOAc (50:1 to 1:1, v/v) to give 5 fractions (E-1-E-5). Fr. E-3 (22.2 g) was further separated by repeated semi-preparative HPLC eluted with CH$_2$CN-H$_2$O (v/v, 75:25, $\nu$ = 1.5 mL/min) to give compound 1 (2.8 mg, $t_R$ = 30.4 minutes).

Isoycretorundone (1): colorless oil; HR-ESI-MS $m/z$ 219.1743 [M + H]$^+$ (calfed for C$_{15}$H$_{22}$O$_4$Na, 275.1620); $\alpha$$_D^{20}$ : +20.8 (chloroform [CHCl$_3$, $\epsilon$ 0.02]); $^1$H-NMR and $^{13}$C-NMR data (CDCl$_3$, 600 and 150 MHz): (Table 1).

1,4-Epoxy-4-hydroxy-4,5-seco-guain-11-ene (2): colorless oil; HR-ESI-MS $m/z$ 275.1618 [M + Na]$^+$ (calfed for C$_{15}$H$_{24}$O$_3$Na, 275.1620); $\alpha$$_D^{20}$ : +80.5 (CHCl$_3$, $\epsilon$ 0.06); $^1$H-NMR and $^{13}$C-NMR data (CDCl$_3$, 600 and 150 MHz): (Table 2).

NF-κB Luciferase Assay

The inhibitory activity of the compounds on TNF-α-induced NF-κB activation was tested with the dual-luciferase assay, as described in our previous publication. 28

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Uddin SJ, Mondal K, Shalpi JA, Rahman MT. Antidiarrhoeal activity of Cyperus rotundus. Fitoterapia. 2006;77(2):134-136. doi:10.1016/j.fitote.2004.11.011
2. Singh N, Kulshrestha VK, Gupta MB, Bhargava KP. A pharmacological study of Cyperus rotundus. Indian J Med Res. 1970;58(1):103-109.
3. Gupta MB, Palit TK, Singh N, Bhargava KP. Pharmacological studies to isolate the active constituents from Cyperus rotundus possessing anti-inflammatory, anti-pyretic and analgesic activities. Indian J Med Res. 1971;59(1):76-82.
4. Zhu M, Luk HH, Fung HS, Luk CT. Cytoprotective effects of Cyperus rotundus against ethanol induced gastric ulceration in rats. Phytother Res. 1997;11(5):392-394. doi:10.1002/(SICI)1099-1573(199708)11:5<392::AID-PTER113>3.0.CO;2-I
5. Sco WG, Pac HO, Oh GS, et al. Inhibitory effects of methanol extract of Cyperus rotundus rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7 cells. J Ethnopharmacol. 2001;76(1):59-64. doi:10.1016/S0378-8741(01)00221-5
6. Dang GK, Parekar RR, Kamat SK, Seindia AM, Rege NN. Anti-inflammatory activity of Phyllanthus emblica, Phyllanthus zeylanica and Cyperus rotundus in acute models of inflammation. Phytother Res. 2011;25(6):904-908. doi:10.1002/ptr.3345
7. Jeong SJ, Miyamoto T, Inagaki M, Kim YC, Higuchi R. Rotundone from Cyperus rotundus. Planta Med. 1997;58(1):103-109. doi:10.1002/(SICI)1099-1573(199708)11:5<392::AID-PTER113>3.0.CO;2-I
8. Kilani S, Abdelwahed A, Ammar RB, et al. Chemical composition, antibacterial and antimutagenic activities of essential oil from (Tunisian) Cyperus rotundus. Journal of Essential Oil Research. 2005;17(6):673-675. doi:10.1080/14786410701193056
9. Sayed HM, Mohamed MH, Farag SF, Mohamed GA, Proksch P. A new steroid glycoside and furochromones from Cyperus rotundus L. Nat Prod Res. 2007;21(4):343-350. doi:10.1080/14786410701193056
10. Sayed HM, Mohamed MH, Farag SF, Mohamed GA, Omubwajo ORM, Proksch P. Fructose-amo acid conjugate and other constituents from Cyperus rotundus L. Nat Prod Res. 2008;22(17):1487-1497. doi:10.1080/1478641080238556
11. Zhou Z, Fu C. A new flavanone and other constituents from the rhizomes of Cyperus rotundus and their antioxidant activities. Chem Nat Compd. 2013;48(6):963-965. doi:10.1007/s10501-013-0439-x
12. Yazdanparast R, Ardestani A. In vitro antioxidant and free radical scavenging activity of Cyperus rotundus. J Med Food. 2007;10(4):667-674. doi:10.1089/jmf.2006.090
13. Jin JH, Lee D-U, Kim YS, Kim HP. Anti-allergic activity of sesquiterpenes from the rhizomes of Cyperus rotundus. Arch Pharm Res. 2011;34(2):223-228. doi:10.1007/s12272-011-0207-z
14. Hemanth Kumar K, Tamata M, Pal A, Khanam F. Neuroprotective effects of Cyperus rotundus on SIN-1 induced nitric oxide generation and protein nitration: ameliorative effect
against apoptosis mediated neuronal cell damage. *Neurotoxicology*. 2013;34:150-159. doi:10.1016/j.neuro.2012.11.002

15. Khojaste M, Yazdanian M, Tahmasebi E, Shokri M, Houshmand B, Shahbazi R. Cell toxicity and inhibitory effects of *Cyperus rotundus* extract on *Streptococcus mutans*, *Aggregatibacter actinomycetemcomitans* and *Candida albicans*. *Eur J Transl Myol*. 2018;28(4):362-369. doi:10.4081/ejtm.2018.7917

16. Mohamed-Ibrahim SR, Mohamed GA, Abdullah Khayat MT, Zayed MF, Soliman El-Kholy AA-E. Anti-inflammatory terpenoids from *Cyperus rotundus* rhizomes. *Pak J Pharm Sci*. 2018;31(4):1449-1456.

17. Wang F, Song X, Ma S, et al. The treatment role of *Cyperus rotundus* L. to triple-negative breast cancer cells. *Biosci Rep*. 2019;39(6):BSR20190502. doi:10.1042/BSR20190502

18. Joseph-Nathan P, Martínez E, Santillan RL, Wesener JR, Günther H. Two-dimensional NMR studies of cypereone. *Org Magn Reson*. 1984;22(5):308-311. doi:10.1002/mrm.1270220507

19. Xu Y, Zhang H-W, Yu C-Y, Lu Y, Chang Y, Zou Z-M. Norcypereone, a novel skeleton norsesquiterpene from *Cyperus rotundus* L. *Molecules*. 2008;13(10):2474-2481. doi:10.3390/molecules13102474

20. Li F, Li C-J, Ma J, et al. Four new sesquiterpenes from the stems of *Pogostemon cablin*. *Fitoterapia*. 2013;86:183-187. doi:10.1016/j.fitote.2013.03.010

21. Hikino H, Aota K, Takemoto T. Structure and absolute configuration of cyperotundone. *Chem Pharm Bull*. 1966;14(8):890-896. doi:10.1248/cpb.14.890

22. Jacobs H, Lachmansing SS, Ramdayal F, McLean S, Puzzuoli FV, Reynolds WF. Applications of 2D-NMR spectroscopy to phytochemical studies: cypereol and cyperenoic acid. *J Nat Prod*. 1987;50(5):835-842. doi:10.1021/np50053a010

23. Hikino H, Aota K, Takemoto T. Structure of sugetriol. *Chem Pharm Bull*. 1967;15(9):1433-1435. doi:10.1248/cpb.15.1433

24. Ryu B, Kim HM, Lee J-S, et al. Sesquiterpenes from rhizomes of *Cyperus rotundus* with cytotoxic activities on human cancer cells *in vitro*. *Helv Chim Acta*. 2015;98(10):1372-1380. doi:10.1002/hlca.201500117

25. Xu F, Morikawa T, Matsuda H, Ninomiya K, Yoshikawa M. Structures of new sesquiterpenes and hepatoprotective constituents from the Egyptian herbal medicine *Cyperus longus*. *J Nat Prod*. 2004;67(4):569-576. doi:10.1021/np030368k

26. Cullmann F, Becker H. Terpenoid constituents of *Pellia epiphylla*. *Phytochemistry*. 1998;47(2):237-245. doi:10.1016/S0031-9422(97)00414-7

27. Sun S-C. The non-canonical NF-κB pathway in immunity and inflammation. *Nat Rev Immunol*. 2017;17(9):545-558. doi:10.1038/nri.2017.52

28. Zeng G-Z, Wang Z, Zhao L-M, Fan J-T, Tan N-H. NF-κB and JNK mediated apoptosis and $G_{0}/G_{1}$ arrest of HeLa cells induced by rubiarbonol G, an arborinane-type triterpenoid from *Rubia yunnanensis*. *J Ethnopharmacol*. 2018;220:220-227. doi:10.1016/j.jep.2017.10.026