Natural products in *Cyperus rotundus* L. (Cyperaceae): an update of the chemistry and pharmacological activities

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1 Introduction

*Cyperus rotundus* L. (Nutgrass, family: Cyperaceae) is a notorious weed which is widespread in temperate and subtropical regions of the world. Owing to its richness and potent pharmacological activities, efforts have been devoted to identify its bioactive constituents. Since 1965, a total of about 192 compounds including terpenoids, flavonoids, stilbenes, aromatics and aliphatic fatty acids have been characterized. This review summarizes the bioactivities and mechanism of action of some of the compounds from *C. rotundus* L.

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1. Introduction

*Cyperus rotundus* (CR) L. (Nutgrass, family: Cyperaceae) popularly called “the world’s worst weed” is widely distributed in subtropical and tropical regions of the world. It is a notorious weed and has a destructive effect on agricultural yields after it invades the crop fields. It is a smooth, erect, glabrous, grass-like, fibrous rooted, perennial herb that grows up to 15–60 cm height (Fig. 1) and reproduces widely through rhizomes and tubers. In Chinese traditional medicine, the rhizomes are used for the treatment of liver diseases, stomach ache, inflammatory diseases, bowel and menstrual disorders. They are also recommended in India for the treatment of diabetes, arthritis, diarrhoea, dysentery, leprosy, bronchitis, amenorrhea, dysmenorrhea, fever, and blood disorders. In West Asia, the roots are applied in traditional medicine for the treatment of leprosy, thirst, fever, and blood diseases. In Egyptian folk medicine, the tubers are used as an anthelmintic, aphrodisiac, diuretic, sedative, carminative, stimulant and tonic, and for treating renal colic and stomach ache. This perennial herb has recently received much attention due to its broad range of pharmacological and biological activities.

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Several reports have stated the presence of terpenoids, flavonoids, stilbene derivatives and other classes of compounds. To the best of our knowledge, a total of about 192 NPs with structural diversity have been isolated from this medicinal weed. Previous reviews have focused on ethnobotanical uses, and pharmacological activities. Also, a majority of researchers have reported in vitro bioactivities and GC-MS analysis of crude extracts of this weed. The objective of the present review was to provide an update of NPs derived from this plant species, their bioactivity and the mechanism of actions of some of the compounds from published data in literature.

2 Data source and preparation

In this review article, a comprehensive search was performed in the following databases: PubMed, SciFinder, Science Direct, Web of Science, Wiley Online, ResearchGate, Google scholar and other search engines were explored for studies published from 1965–2020. Keywords such as: “C. rotundus”, ‘bioactive compounds’, and “pharmacological activities” were used. We removed duplicated papers, then screened the data, ruled out irrelevant publications. The focus was on research or review articles, work on NPs isolated from this weed. Many of the publications were focused on isolation, structure elucidation and pharmacological activities.

3 Natural products derived from C. rotundus L. species

After decades of detailed phytochemical investigation, it is evident that this plant species contains two major classes of secondary metabolites, namely, terpenoids and flavonoids
mostly harvested from Asia and Africa (Fig. 2). 8,12,13,17,40,79–87,89–94,112–119

3.1 Terpenoids

To date, a total of about 131 terpenoids (1–131) have been isolated and identified from *C. rotundus* (CR) (Fig. 3–7). The summaries of the most interesting results for terpenoids isolated from CR have been shown in Table 1. Sesquiterpenes are the major subclass of NPs isolated from this herb. A majority of the secondary metabolites were isolated from the rhizomes/tubers of the plant and they are structurally related, for example, (1–117). 31,120 α-Cyperone (17) isolated from the n-hexane fraction significantly inhibited prostaglandin E2 (PGE2) production by suppressing lipopolysaccharide (LPS)-induced expression of inducible cyclooxygenase-2 (COX-2) at both RNA and the protein levels. 121 Compound 17 obtained from the tubers of this plant species also showed insecticidal activity. 122 Isocyperol (18) has been found to significantly inhibit LPS-induced production of nitrite oxide (NO), PGE2 and suppressed LPS-induced expression of inducible nitric oxide synthase (iNOS) and COX-2 at the mRNA and protein levels in RAW 264.7 macrophages. 123 Extraction of air-dried and chopped rhizomes of CR with hot 70% EtOH followed by purification using GC-MS afforded monoterpenes, sesquiterpenes and
aromatic compounds (10, 17, 37–43). The sesquiterpenes; valencene (10) and (+)-nootkatone (40) significantly inhibited inducible nitric oxide (iNOS) expression and nitric oxide (NO) production in LPS-simulated RAW264.7 cells. The anti-inflammatory mechanism of CR is due to heme oxygenase-1 (HO-1) induction by compounds 10 and 40. While (+)-nootkatone (40) has been found to have potent inhibitory effect on collagen-, thrombin-, and AA-induced platelet aggregation. Compound 40 was treated with mice and it exhibited significant prolonged bleeding times. It has also shown significant inhibitory effect on rat platelet aggregation *ex vivo*.77

Three novel sesquiterpene alkaloids; rotundines A (44), B (45), and C (46) were isolated from the MeOH extract using standard methods of extraction of alkaloids. The structures of the compounds were determined by comprehensive spectroscopic analyses and chemical methods.15

Ohira et al.82 isolated the new sesquiterpenoids; 2α-(5-oxopentyl)-2β-methyl-5β-isopro-penlycyclohexanone (48), 2β-(5-oxopentyl)-2β-methyl-5β-isopropylcyclohexanone (49), cyperolone (50) together with the known compounds 17, 19, 40, 51 and 52 from the roots of CR. The antibacterial activities of the new hits were screened against *Escherichia coli* and *Bacillus subtilis* using the paper disk method. Cyperolone (50) possessed moderate activity against *B. subtilis* at a concentration of 0.5 mg per disk; the other compounds did not show notable activities.82

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Fig. 4 Structures of terpenoids isolated from *Cyperus rotundus* (35 to 61).
The new sesquiterpenes, cyperusol A3 (53), 3β-hydroxyycyperenoic acid (54), along with three known compounds (55–57) were isolated from the ethyl acetate soluble fraction of the rhizomes using a series of column chromatography. The compounds were submitted for their cytotoxic activities against human ovarian cancer cells (A2780) and endometrial adenocarcinoma cells (Ishikawa) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assays and 11,12-dihydroxyeudesm-4-en-3-one (57) showed the most potent cytotoxic activity with observed IC50 values of 11.06 and 6.46 mm, respectively.\(^\text{12}\)

Jin et al.\(^\text{10}\) isolated the known compounds; valencene (10), α-cyperone (17), β-pinene (37), limonene (38), 4-cymene (39), (+)-nootkatone (40), 1,8-cineole (41), caryophyllene oxide (42), and β-selinene (43) and evaluated them for their anti-allergic activity in vitro and in vivo. In rat basophilic leukemia (RBL)-1 cells, the sesquiterpenes (10, 40, 42) were reported to strongly inhibit 5-lipoxygenase-catalyzed leukotrienes production. In addition, they inhibited β-hexosaminidase release by antigen-

Fig. 5 Structures of terpenoids isolated from *Cyperus rotundus* (62 to 94).
stimulated RBL-2H3 cells, with valencene having the highest inhibitory effect. Authors also found that the most active sesquiterpene (10) inhibited β-hexosaminidase degranulation by inhibiting the initial activation reaction, Lyn phosphorylation, in IgE-stimulated RBL-2H3 cells. Moreover compounds (10, 40), significantly inhibited the delayed-type hypersensitivity reaction in mice when administered orally at 50–300 mg kg\(^{-1}\).  

The isolation of cyperolone (50) from the essential oil of CR, rekindled the interest of NP Chemists to revisit this plant species. Investigation of the constituents from Chinese origin, led to the isolation of known compounds (19, 50) and new sesquiterpenes; copadiene (58), epoxyguaien (59), rotundone (60) and 4α,5β-oxidoeudesm-11-en-3β-ol (61).  

Bioactivity and liquid chromatography-mass spectrometry (LC-MS) guided fractionation of 90% EtOH extract using open-column, Sephadex LH-20 and semi-preparative high performance liquid chromatography (HPLC) led to the isolation and identification of thirty-seven sesquiterpenoids.  

The compounds include, five new patchoulane-type sesquiterpenoids, 3β-hydroxyperpenoic acid (54), cyperene-3,8-dione (62), 14-hydroxyperotundone (63), 14-acetoxysterotundone (64) and sugetriol-3,9-diacetate (65) along with the known NPs 4, 17, 20, 27, 36, 51 and 66–89. Nine eudesmane-type sesquiterpenoids (20, 71–77 and 78–80) significantly inhibited the hepatitis B virus (HBV) DNA replication with IC\(_{50}\) values of 42.7 ± 75.9, 22.5 ± 71.9, 13.2 ± 71.2, 10.1 ± 70.7, 14.1 ± 71.1, 15.3 ± 72.7, 13.8 ± 70.9, 19.7 ± 72.1 and 11.9 ± 70.6 µM, respectively, of which, compounds 72, 76, 78 and 80 possessed high selectivity index (SI) values of 250.4, 125.5, 259.6 and 127.5, respectively. Two patchoulane-type sesquiterpenoids (54 and 36) effectively suppressed the secretion of HBsAg in a dose-dependent manner with IC\(_{50}\) values of 46.6 ± 714.3 (SI = 31.0) and 77.2 ± 713.0 (SI = 1.7) µM, respectively. Compounds 63, 4, 17, 20, 72 and 81 possessed moderate activities against HBeAg secretion with IC\(_{50}\) values of 162.5 ± 718.9 (SI = 13.3), 399.2 ± 790.0 (SI = 10.6), 274.7 ± 770.8 (SI = 5.2), 313.9 ± 787.5 (SI = 7.2), 334.0 ± 770.4 (SI = 9.9) and 285.3 ± 720.9 (SI = 15.5) µM, respectively.  

Antimalarial activity-guided investigation and HPLC separation of the crude hexane extract of CR tubers led to the isolation of the sesquiterpenes; 42, patchoulenone (90) and 10,12-peroxycalamenene (91). The antimalarial activities of these compounds were determined from their effective concentrations (EC\(_{50}\)) values against *Plasmodium falciparum*. The *in vitro* activity against *P. falciparum* (EC\(_{50}\)) of compounds...
90 and 91 were in the order of $10^{-4}$ M (1.08 $\times$ 10$^{-4}$ and 3.45 $\times$ 10$^{-4}$ M respectively).

Chemical investigation of the rhizomes of CR led to the isolation of a new norsesquiterpenes, named norcypereone (92), (-)-clovane-2,9-diol (93) and other known compounds. The structure of the novel norsesquiterpene (92) with a tetrahydrofuran ring structure was established on the basis of extensive spectroscopic analyses, including 1D- and 2D-NMR, MS experiments, and single-crystal X-ray diffraction.

A novel norsesquiterpenoid named cyperalin A (94) with the known compound (27) were isolated from freshly-cut rhizomes of CR defatted with n-hexane followed by extraction with methanol and silica gel chromatography. The compounds were screened for their anti-inflammatory activity. Cyperalin A (94) displayed the highest inhibitory activity of PGE2, COX-2, and LOX-5 with IC$_{50}$s 0.22, 1.03, and 1.37 µM, respectively compared to indomethacin (IC$_{50}$s 0.15, 0.69, and 0.81 µM, respectively). Compound 27, showed significant activity with IC$_{50}$s 0.57 (PGE2), 1.74 (COX-2) and 2.03 (LOX-5) µM.

The new sesquiterpenes, 4x,5x-oxidodesm-11-en-3-one (95) and cyper-11-ene-3,4-dione (96) together with the known compounds 4, 17, 18 and 47 were obtained from the hexane and dichloromethane fractions of CR. The compounds were examined for their estrogenic activity by E-screen assay on MCF-7 BUS cells. Compound 2, exhibited the most potent estrogenic activity by increasing transcriptional activities in an estrogen sensitive reporter gene assay. The authors showed that compound 2, has biphasic activities on estrogen receptors which could be useful as an alternative hormone replacement therapy. Compounds 4 and 17 isolated from the tubers of CR have showed growth inhibitory effects to both shoots and roots on the lettuce seedlings.

Rani et al. isolated the sesquiterpenes 40; solavetivone (97) and aristolone (98) from the acetone extract of CR by silica gel column chromatography and determine their radical scavenging potential compared with standard gallic acid. Among the three sesquiterpenoids isolated, compound 40 possessed the highest radical scavenging potential (IC$_{50}$ 4.81 g mL$^{-1}$) followed by 98 (IC$_{50}$ 5.28 g mL$^{-1}$) and the new compound 97 (IC$_{50}$ 6.82 g mL$^{-1}$) by DPPH radical scavenging assay.

Bioassay-guided fractionation of the methanol extracts of the rhizomes of CR led to the isolation of 41, 42, zerumbone (99), x-
Table 1  Summary of the bioactivity of derived terpenoids from *Cyperus rotundus*<sup>a</sup>

| Compounds          | Part(s)/place of harvest of plant studied (VS #) | Measured activity | References            |
|--------------------|-----------------------------------------------|-------------------|-----------------------|
| Rotundene (1)      |                                               |                   |                       |
| 1, (−)-cypera-2,4-diene (2), cyproteine (3), cyperotundone (4), (+)-cyperadione (5), (−)-norrotundene (6), (−)-isorotundene (7), γ-gurjunene (8), nootkatene (9), valencene (10), *epi*-α-selinene (11), α-muurolene (12), γ-muurolene (13), ylanga-2,4-diene (14), γ-calacorene (15), cadalene (16), α-cyperone (17), isocyperol (18), mustakone (19) and cyperol (20) and (−)-cypera-2,4(15)-diene (21) 3,4-O-isopropylideneshikimic acid (22), rotundusolide A (23), rotundusolide B (24), dehydrocostus lactone (25), (+)-alismoxide (26), sugetriol triacetate (27), 2β-hydroxy-2-cyperene (28), eudesma-4(14),11(13)-diene–7α,8α,12-triol (29), rotundusolide C (30), secomacrogenin B (31), and 3,4-seco-mansumbinoic acid (32) | Rhizomes/Purchased from Lanzhou Traditional Chinese Medicine Market (no. ZY2009C002) | ND | Yang et al.,<sup>49</sup> |
| 4, 27, *Epi*-guaidiol A (33), guaidiol A (34), sugebil (35) and cyperenoic acid (36) |                                               |                   |                       |
| 10, 17, β-pinene (37), limonene (38), 4-cymene (39), (+)-nootkatone (40), 1, 8-cineole (41), caryophyllene oxide (42), β-selinene (43) | Rhizomes/Da-Bie-Shan Mountains, Anhui province, China. (No: 20060825) Rhizomes/Purchased from Kyung Dong market place in Seoul, South Korea. (DKH-02561) | Anti-inflammatory activity | Tsoyi et al.,<sup>17</sup> |
| 10, 17, 37- 43 18 |                                               |                   |                       |
| 17 |                                               |                   |                       |
| Rotundene A (44), rotundene B (45), and rotundene C (46) |                                               |                   |                       |
| α-Cyperene (47)    |                                               |                   |                       |
| 17, 19, 40, 2α-(5-oxopentyl)-2β-methyl-5β-isopropenylcyclohexanone (48), 2β-(5-oxopentyl)-2β-methyl-5β-isopropenylcyclohexanone (49), cyperolene (50), α-rutunol (51) and β-rutunol (52) |                                               |                   |                       |
| Cyperusol A<sub>1</sub> (53), 3β-hydroxy-cyperene acid (54), britanlin E (55), 1β, 4α-dihydroxyeudesm-11-ene (56) and 11,12-dihydroxyeudesm-4-en-3-one (57) |                                               |                   |                       |
| 10, 37-42 |                                               |                   |                       |
| Copadiene (58), epoquyauien (59), and rotundone (60) 19 |                                               |                   |                       |
| 50 |                                               |                   |                       |
| 4α,5β-oxidoeudesm-11-en-3α-ol (61) 51 and 52 |                                               |                   |                       |
| 4, 17, 20, 27, 36, 51, 54, cyperene-3,8-dione (62), 14-hydroxy-cyperotundone (63), 14-acetoxycyperotundone (64), sugetriol-3,9-diacetate (65), cyperol (66), sugenol (67), scaridione (68), (4αS, 7S)-7-hydroxy-1,4a-dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronephthalen-2(3H)-one (69), (4αS, 7S, 8R)-8-hydroxy-1,4a-dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7-hexahydronephthalena-2(3H)-one (70), 1β-hydroxy-α-cyperone (71), 10-eupiedesm-11-ene-3β, 5α-diol (72), 3β-hydroxylicic alcohol (11(13)-eudesmen-3,4,12-triol) (73), cypercol C (74), α-corymbolet (75), 3β, 4α-dihydroxy-7-epi-eudesm-11(13)-ene (76), 2-oxo-α-cyperone (77), 7α (H), 10β-eudesm-4-en-3-one-11,12-diol (78), 2-hydroxy-14-calamenone (79), rhombitriol (80), 7-epi-teucrenone (81), 12-hydroxynootkatone (82), | Rhizomes/Purchased from Juhiacun (Kunning, China) (no. 2011041101) | Anti-hepatitis B virus activity | Xu et al.,<sup>11</sup> |
Table 1 (Contd.)

| Compounds                                                                 | Part(s)/place of harvest of plant studied (VS#)                                                                 | Measured activity          | References                        |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------------------|
| olopanone (83), 10-hydroxyamorph-4-en-3-one (84), cyperosol D (85), argustosine D (86) and 4,5-seco-guaia-1\(\beta\)-dien-4,5-dioxy (87), oxyphyllol C (88) and 5-hydroxylucinone (89) | Tubers/Purchased from a Thai traditional dispensary, Bangkok, Thailand                                           | Antimalarial activity      | Thebtaranonth et al., 83          |
| 42, patchoulenone (90) and 10,12-peroxyxalamene (91)                        | Rhizomes/Dabieshan Mountains of Anhui Province, P.R. China (no: 20060825)                                        | ND                         | Xu et al., 84                     |
| Norcyperone (92) and \((--\)clove-2,9-diol (93)                               | Rhizomes/King Abdulaziz University campus, Jeddah, Saudi Arabia (2014-CR110)                                     | Anti-inflammatory activity  | Ibrahim et al., 93                |
| 27 and cypertin A (94)                                                      | Rhizomes/purchased from Kyungdong-Yakryongsi traditional medicine market in Seoul, Korea (SKKU-PP-12:50)           | Estrogenic activity        | Park et al., 94                   |
| 4, 17, 18, 47, 42, 5a-oxidoedems-11-en-3-one (95) and cypdr-11-ene-3,4-diene (96) | Rhizomes/obtained from a registered medicinal plant vendor in Trivandrum (no. 034/2011)                          | Antioxidant activity       | Rani et al., 97                   |
| 40, solavetione (97) and aristolone (98)                                    | Tubers/Bogor-Indonesia/NM                                                                                      | Insecticidal activity      | Dadang et al., 122                |
| 17                                                                        | Rhizomes/Purchased from the Boeun medicinal herb shop (Seoul Yangnyeongsi, Seoul, South Korea) (CR-01)             | Repellent activity         | Chang et al., 92                  |
| 4, 17, 20, 43, 47, 101, 109, \beta-elemene (111), caryophyllene (112), \beta-cadinene (113), calamenene (114), patchoulenyl acetate (115) and \(6\)-acetoxy-patchoul-4-en-3-one (116) Cyprotuside A (117) and cyprotuside B (118) | Rhizomes/supplied by Morihiro Kinoshita (Nihon Funmatsu Yakuhin Company, Japan) (NM)                           | Phytotoxicity              | Morimoto et al., 128              |
| 18-Epi-\(\beta\)-amyrin glucuronoside (119), oleanolic acid arabinoside (120), \(\beta\)-amyrin glucopyranoside (121) and \(\beta\)-amyrin glucopyranoside (122) | Tubers/Islands of Oahu, Maui, Kauai and Hawaii (NM)                                                           | ND                         | Komai et al., 80                  |
| Oleanolic acid (123), oleanolic acid-3-O-neohesperidoside (124) and \(\beta\)-sitosterol (125) | Rhizomes/Zhanjiang, Guangdong Province of China (No.20090903)                                                   | Antidepressant activity    | Zhou et al., 90                   |
| 12-Methyl cyprot-3-en-2-one-13-oic acid (126), stigmastrol-\(\beta\)-dodecanoate (127), stigmastrol-\(\beta\)-tetradecanoate (128), \(\beta\)-sitosterol glucoside (129) and lupenyl arabinopyranosyl oleate (130) Sitosteryl (131) | Tubers/University of Allahabad campus, Allahabad, India (NM)                                                     | ND                         | Alam et al., 86                   |
| Aerial parts/El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt.                                      | Tubers/Purchased from a Delhi market                                                                            | Antifeedant and Cytotoxic activity | Sultana et al., 91                |

* VS#: Voucher specimen number, NM: not mention, ND: not done.

The compounds were tested for repellency to male *Blattella germanica* and the results were compared to *N*-diethyl-3-methylbenzamide (deet). In filter-paper choice tests, 99 was the most repellent compound, and 100 was ineffective, which shows that \(\alpha\),\(\beta\)-unsaturated carbonyl group of 99 contributes to repellency. The article reported that at 81.5 µg
cm$^{-2}$, enhanced repellency was produced by binary mixtures of 99 and 41, 101 or 102 (70 : 30, 50 : 50 and 30 : 70 ratios by weight). In Ebeling choice box tests at 652.4 µg cm$^{-2}$, these compounds and deet resulted in complete repellency to intact male B. germanica, while they exhibited 35–47% repellency to antennectomized male one. Mixtures of active compounds from this plant species could serve as potential repellents for controlling B. germanica.92

A series of mono and sesquiterpenoids, 4, 17, 20, 43, 47, 101, 109, β-elemene (111), carophyllene (112), δ-cadinene (113), calamenene (114), pachoulolyl acetate (115) and sugeonyl acetate (116) were isolated from the mature tubers of CR using gas chromatography-mass spectrometry (GC-MS). A new chemotype of CR was found in Hawaii based on the sesquiterpene composition of the mature tubers. The K-type has higher concentrations of 115 and 116 than the three known Asian chemotypes. Information on the distribution of chemotypes could also offer clues to the history of spreading CR weed species.90

Zhou et al.90 isolated the two novel cycloartane glycosides, cyprotuside A (117) and cyprotuside B (118) from the rhizomes of CR and evaluated their antidepressant activity by forced swimming test (FST) and tail suspension test (TST) in mice. The preliminary in vivo evaluation showed that compounds 117 and 118 exhibited remarkable antidepressant activity in the despair mice models.

Exhaustive extraction of air-dried powdered tubers of CR with methanol followed by chromatography over silica gel column and elution with a gradient of chloroform and methanol afforded two new triterpenic glucosides; 18-epi-α-amyrin glucuronoside (119), oleanolic acid arabinoside (120), and α-amyrin glucopyranoside (121) and β-amyrin glucopyranoside (122).96

The sesquiterpenoid, 12-methyl cypro-3-ene-2-one-13-oic acid (126), steroidal esters; stigmasterol-n-dodecanoate (127), stigmasteryl-n-tetradecanoate (128), β-sitosterol glucoside (129) and triterpenoid glucosides; lupenyl arabinopyranosyl olate (130) were isolated for the first time and they could serve as chromatographic markers for standardization of the tubers of CR.96 A new steroid glycoside; sitosteryl (131) and other compounds were also isolated from the aerial parts of this plant species harvested in Egypt.91

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Table 2  Summary of the bioactivity of derived flavonoids from Cyperus rotundus$^a$

| Compounds | Part(s)/place of harvest of plant studied (VS#) | Measured activity | References |
|-----------|-----------------------------------------------|-------------------|------------|
| Luteolin-7-O-glucoside (132), tricin (133) and auresudin (134) | Leaves/stem, Australia [K. L. Wilson 3309] (Denistone, N.S.W) | ND | Harborne et al.141 |
| Azelechin (135), (+)-catechin (136), luteolin (137), and queretin (138) | Aerial parts/Monastir region in the Center of Tunisia (Cp.10.04) | Antioxidant and antitumor activities | Kilani-Jaziri et al.40 |
| Rutin (139) | Rhizomes/Al-Azhar University campus, Assiut Branch, Egypt (2009-CR110) | Hepatoprotective activity | Mohamed,78 |
| Pongamone A (140) and biochanin A (141) | Rhizomes/Collected in Zhanjiang, Guangdong Province of China (No.20090903) | ND | Zhou et al.11 |
| 137 | Rhizomes/Purchased from Matsuura-Yakugyo Co. Ltd. (Nagoya, Japan) CP-0901 | Antiproliferative activity | Ito et al.18 |
| 133, isorhamnetin (142), vitexin (143), isovitexin (144), orelintin (145), epiorientin (146), myricetin-3-O-β-D-glucuronopyranoside (147), luteolin-7-O-β-D-glucuronopyranoside-6′-methyl ester (148), luteolin-4′-O-β-D-glucuronopyranoside (149) and Luteolin-7-O-β-D-glucuronopyranoside (132) | Aerial parts/Experimental Station of El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt | Antioxidant and α-amylase inhibitory activities | Sayed et al.8 |
| 133 and 143 | Aerial parts/Experimental Station of El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt (NM) | Antifeedant and Cytotoxic activity | Sayed et al.33 |
| 143, 145, cinaroside (150), quercetin-3-O-β-D-glucuronopyranoside (151), cyperaflavoside (152) and myricetin-3′-O-β-D-glucuronopyranoside (153) | Aerial parts/King Abdulaziz University campus, Jeddah, Saudi Arabia (2014-CR110) | 5-Lipoxygenase inhibitory activity | Ibrahim et al.93 |

$^a$ VS#: Voucher specimen number, NM: not mention, ND: not done.
3.2 Flavonoids

Flavonoids continue to attract attention as potentially useful compounds because of their broad spectrum of biological activities. In this report, summaries of the most interesting results for flavonoids (132–153) isolated from CR have been shown in Table 2, while the chemical structures of the isolated compounds are shown in Fig. 8 and 9. In Table 2, the biological activities of the compounds and the organism studied have been provided.

Harborne et al. isolated luteolin-7-O-glucoside (132), tricin (133) and aureusidin (134) from the leaves/stems of CR by paper electrophoresis. The structures of the compounds were identified by standard procedures and co-chromatography with authentic samples carried out in at least 4 solvents.

In an effort to search for novel antioxidant and anti-proliferative hits, four flavonoids; afzelechin (135), (+)-catechin (136), luteolin (137), and quercetin (138) and other compounds were isolated from the total oligomers flavonoids and ethyl acetate extracts of CR. Compound 137 was the most active in reducing the production of thiobarbituric acid reactive substances (malondialdehyde = 1.5 nM), inhibiting significantly the proliferation of K562 cells (IC50 = 25 g mL−1) and protecting against H2O2/UV-photolysis induced DNA damage. Rutin (139), pongamone A (140) and biochanin A (141) were

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Fig. 8 Structures of flavonoids isolated from Cyperus rotundus (132 to 149).
isolated from the rhizomes of this plant species and the structure was established on the basis of 1D and 2D NMR spectroscopic analyses.\textsuperscript{15,79} Luteolin (137) has been isolated from the rhizomes of this plant species.\textsuperscript{18}

Table 3 Summary of the bioactivity of derived stilbenes and derivatives from *Cyperus rotundus\textsuperscript{\textdagger}

| Compounds                        | Part (s)/place of harvest of plant studied (VS \#)                                                                 | Measured activity                                                                 | References                   |
|----------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------|
| (+)-Cyperusphenol A (154), (−)-(E)-cyperusphenol A (153), (E)-mesocyperusphenol A (156), cyperusphenol C (157), cyperusphenol B (158), cyperusphenol D (159), trans-scirpusin A (160) and scirpusin B (161) | Rhizomes/Purchased from Matsuura-yakugyo Co. Ltd. (Nagoya, Japan) (CP-0901)                                                | Antiproliferative activity                                               | Ito et al.,\textsuperscript{18} |
| 4,7-Dimethyl-1-tetralone (162)   | Tubs/Purchased from a Thai traditional dispensary, Bangkok, Thailand                                         | Antimalarial activity                                                         | Thebtaranonth et al.,\textsuperscript{81}|
| p-Hydroxybenzoic acid (163)      | Rhizomes/Purchased from Uchida Wakanyaku Co., Ltd. (Tokyo, Japan) (lot. 242118)                              | ND                                                                              | Jeong et al.,\textsuperscript{15} |
| Salicylic acid (164), caffeic acid (165), protocatechuic acid (166) and p-coumaric acid (167) and ellagic acid (168) | Aerial parts/El-Safa and El-marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt                  | Antifeedant and Cytotoxic activity                                         | Sayed et al.,\textsuperscript{33} |
| 164–167, methoxyperrotundol (169) and perrotundol (170) | Rhizomes/Collected in Zhanjiang, Guangdong Province of China (no. 20090903)                                      | Anti-inflammatory activity                                                    | Tsyo et al.,\textsuperscript{17} |
| Galloyquinic acid (171), 3-hydroxy-4-methoxybenzoic acid (172) and ferulic acid (173) | Aerial parts/Monastir region in the Center of Tunisia (Cp.10.04)                                               | Antioxidant and antitumor activities                                       | Kilani-Jaziri et al.,\textsuperscript{40} |
| Chlorogenic acid (174)           | Rhizomes/obtained as Organic Musta Powder (Khandige Organic Health Product, Bangalore, India) (NM)           | Anti-inflammatory activity                                                    | Rocha et al.,\textsuperscript{10} |
| Methyl-3,4-dihydroxybenzoate (175) | Rhizomes/Al-Azhar University campus, Assiut Branch, Egypt (2009-CR110)                                        | Hepatoprotective activity                                                   | Mohamed,\textsuperscript{78} |

\textsuperscript{\textdagger}VS \#: Voucher specimen number, NM: not mention, ND: not done.
Fig. 10 Structures of stilbenes, ellagic acid derivatives and other compounds from *Cyperus rotundus* (154 to 170).

Fig. 11 Structures of stilbenes and derivatives isolated from *Cyperus rotundus* (171 to 175).
Table 4  Miscellaneous compounds from Cyperus rotundus\textsuperscript{a}

| Compounds | Part(s)/place of harvest of plant studied (VS\#) | Measured activity | References |
|-----------|---------------------------------------------|------------------|------------|
| n-Butyl-\(\alpha\)-\(\alpha\)-fructopyranoside (176), ethyl-\(\omega\)-\(\omega\)-glucopyranoside (177), adenosine (178) and (−)-(\(E\))-cafeoylmalic acid (179) | Aerial parts/Experimental Station of El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt | Antioxidant and \(\alpha\)-amylase inhibitory activities | Sayed et al.,\textsuperscript{8} |
| Benzo-\(\alpha\)-pyrone (180), khellin (181), visnagin (182), ammiol (183) and khellol-\(\beta\)-\(\beta\)-glucopyranoside (184) | Aerial parts/El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt | Antifeedant and Cytotoxic activity | Sayed et al.,\textsuperscript{33} |
| Ipomamiide (185) and 6\(\beta\)-hydroxipyrolamidine (186) | Rhizomes/Al-Azhar University campus, Assiut Branch, Egypt (2009-CR110) | Hepatoprotective activity | Mohamed,\textsuperscript{78} |
| 1-O-(\(\beta\)-\(\beta\)-glucopyranosyloxy)-\(2S,3R,4E,8Z\)-2\(\prime\)-(\(2R\)-2\(\prime\)-hydroxylignoceranoylamino)-4,8-tetradecene-3-diol (187) | Radix/Shandong, China | Anti-proliferation activity | Liu et al.,\textsuperscript{143} |
| n-Tricort-1-ol-21-one (188) | Tubers/West Champaran, Bihar, India (No.NISCAIR/RHMD/Consult/-2008-09/1114/145) | ND | Alam et al.,\textsuperscript{86} |
| Succinic acid (189), myristic acid (190), palmitic acid (191) and stearic acid (192) | Tubers/upland rice fields (sandy loam soil) of Manikganj district, Bangladesh (NM) | Growth inhibitory effects | Quayyum et al.,\textsuperscript{144} |

\textsuperscript{a} VS\#: Voucher specimen number, NM: Not mention, ND: Not done.

Fig. 12  Structures of miscellaneous compounds isolated from Cyperus rotundus (176 to 192).
3.3 Stilbenes and derivatives

Stilbenes are polyphenols containing resveratrol as a basic subunit. These compounds have received much attention because of their cardioprotective effects, but they also display anti-inflammatory, antioxidative, and antimicrobial activities. They are also known as anticancer and cancer-chemopreventive agents. The stilbenes and derivatives (154–176) isolated from CR by several NP research groups have shown interesting biological activities during in vitro screening exercise (Table 3).11,17,40,77,78,110 The chemical structures of those isolated from this herb are shown in Fig. 10 and 11.

The novel enantiomeric and meso-stilbene trimers; (+)-cyperusphenol A (154), (−)-(E)-cyperusphenol A (155), (E)-mesocyperusphenol A (156), a trimer bearing a novel hexacyclic ring system, cyperusphenol B (158), together with the known stilbenoids, cyperusphenol C (157), cyperusphenol D (159), trans-scirpusin A (160) and scirpusin B (161) were isolated from the rhizomes of CR. The hits were evaluated for their anti-proliferative activity employing the Jurkat cell line (human T-cell leukemia cells), while the IC50 potencies of a racemate of compounds 154–156, 158, and 159 were estimated as 27.4, 40.5, 26.4, and 26.3 μM, respectively. The article reported that the suppression of cell growth by compound 159 was due to the induction of apoptosis, which was characterized by nuclear changes and PARP-1 cleavage determined by western blotting. Salicylic acid (164), caffeic acid (165), protocatechuic acid (166) and p-coumaric acid (167) isolated from this weed showed significant antioxidant activity. The insect antifeedant activity demonstrated by the crude extracts is due to the presence of furochromones having methoxyl group at positions C-5 and/or C-8 positions.

3.4 Miscellaneous compounds

Steroidal glycosides, furochromones and aromatics (177–185) isolated from the aerial parts of CR collected from Egypt demonstrated antioxidant, α-amylase inhibitory and antifeedant activities. A summary of these bioactive compounds isolated from CR is provided in (Table 4) and their chemical structures in Fig. 12. New iridoids, cerebroside, known aliphatic fatty acids and coumarin (186–192) from this plant species have also shown hepatoprotective, anti-inflammation, and growth inhibitory properties respectively.

3.5 Bioactivities and proposed mechanisms of C. rotundus compounds

The pharmacological activities and mechanisms of action of some compounds isolated from C. rotundus have been reported extensively.8,11,17,41,76–78 The summaries of the most interesting results for some NPs isolated from this weed have been shown in Fig. 12.

Conclusions

Cyperus rotundus L. (Nutgrass, family Cyperaceae) popularly called “the world’s worst weed” has attracted particular attention as a medicinal plant, due to its broad spectrum of pharmacological activities. In the past six decades, about 192 NPs have been isolated and characterized from this plant species. Among them, terpenoids and flavonoids are the major bioactive constituents mostly harvested from Asia and Africa. The chemical structures of pure compounds were retrieved from literature sources comprising data collected from articles from major peer-reviewed journals, from all over the world spanning the period 1965 to 2020. The collected data includes region of collection of plant material, voucher specimen number, isolated metabolites and class, and measured biological activities of isolated compounds. The study has provided a survey of the biological activities of 192 NPs and the mechanism of action of some of the compounds isolated from C. rotundus. It is worth mentioning that C. rotundus and its NPs have shown good safety in vitro and in vivo studies. Thus it would be interesting in future to evaluate the toxicities of the NPs from this weed using in silico approaches.

Conflicts of interest

There are no conflicts to declare.

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