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

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Cyperus rotundus L. (Nutgrass, family Cyperaceae) is a notorious weed which is widespread in temperate tropical 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.

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.[1–3] It is a notorious weed and has a destructive effect on agricultural yields after it invades the crop fields.[4,5] 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.[6] In Chinese traditional medicine, the rhizomes are used for the treatment of liver diseases, stomach ache, inflammatory diseases, bowel and menstrual disorders.[7–13] They are also recommended in India for the treatment of diabetes, arthritis, diarrhoea, dysentery, leprosy, bronchitis, amenorrhea, dysmenorrhea, fever, arthritis and blood disorders.[14–16] In West Asia, the roots are applied in traditional medicine for the treatment of leprosy, thirst, fever, and blood diseases.[17,18] In Egyptian folk medicine, the tubers are used as an antihelmintic, aphrodisiac, diuretic, sedative, carminative, stimulant and tonic, and for treating renal colic and stomach ache.[19] This perennial herb has recently received much attention due to its broad range of pharmacological and biological activities.[5,20–75]

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Aurélien F. A. Moumbock received both BSc (2013) and MSc (2017) degrees in Chemistry at the University of Buea (Cameroon). Since 2018, he is carrying out doctoral studies in pharmaceutical sciences at the University of Freiburg (Germany) under the guidance of Profs Stefan Günther and Henning J. Jessen, with a fellowship from the German Academic Exchange Service (DAAD). His research focuses on the development and application of chemoinformatics methods and tools to accelerate (nature-inspired) small-molecule drug discovery.

Fig. 1 Photograph of the plant *Cyperus rotundus* L. (Cyperaceae).

Several reports have stated the presence of terpenoids, flavonoids, stilbene derivatives and other classes of compounds.[8,11,17,41,76–78] To the best of our knowledge, a total of about 192 NPs with structural diversity have been isolated from this medicinal weed.[8,12,13,17,41,79–94] Previous reviews have focused on ethnobotanical uses, and pharmacological activities.[6,71,95,96] Also, a majority of researchers have reported *in vitro* bioactivities and GC-MS analysis of crude extracts of this weed.[2,14,41,97–111] 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.

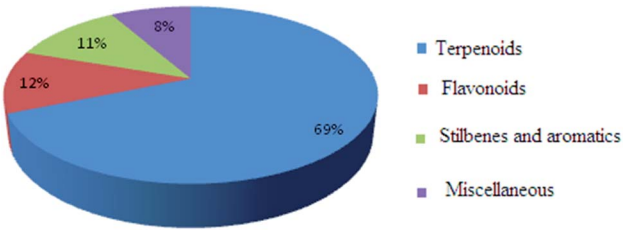


Fig. 2 Pie chart showing the distribution by compound class.

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

Dr Stefan Günther studied biology and informatics in Germany and was appointed to a JuniorProfessor in Pharmaceutical Bioinformatics in 2009 and to a Full Professor in 2015 at the University Freiburg, Germany. His research area is the development and application of methods from bioinformatics in pharmaceutical sciences. He has a special focus on structure-based drug discovery and the prediction of theeffects of natural products for therapeutic application.

Fidele Ntie-Kang heads the Molecular Simulations Laboratory, Chemistry Department, University of Buea. He studied Chemistry at the University of Douala (Cameroon) from 1999 to 2005, leading to Bachelor's and Master's degrees. His PhD from University oof Douala (Caeroon) was based on molecular modeling of anti-tubercular drug target to design novel inhibitors, followed by an Habilitation in Pharmaceutical Chemistry from Martin-Luther University Halle-Wittenberg (Germany), under the supervision of Prof. Wolfgang Sippl. His current focus is the discovery of bioactive natural products from African flora by the use of virtual screening followed by in vitro assays. A major contribution of his research team has been the development of the African natural products database.

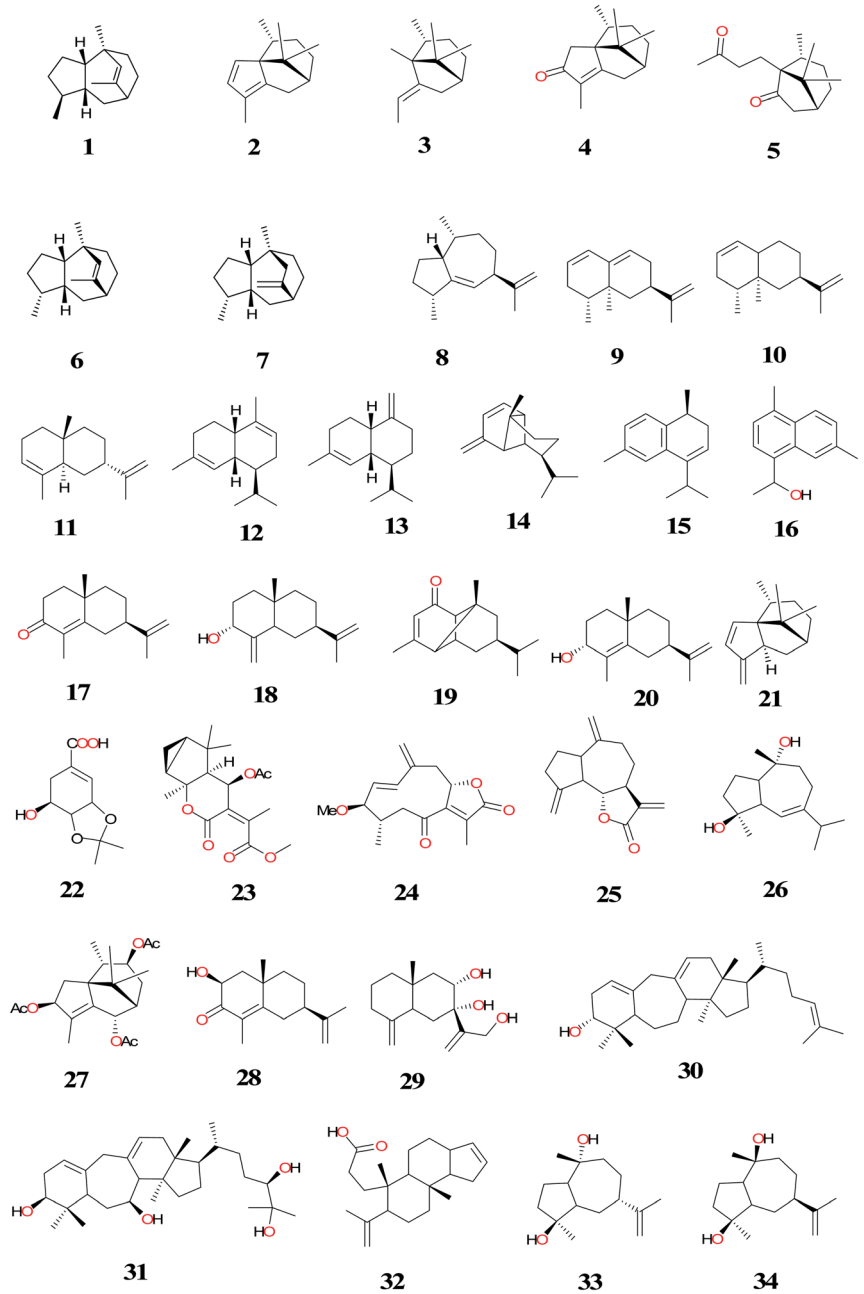


Fig. 3 Structures of terpenoids isolated from *Cyperus rotundus* (**1** to **34**).

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**).[83,120] 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

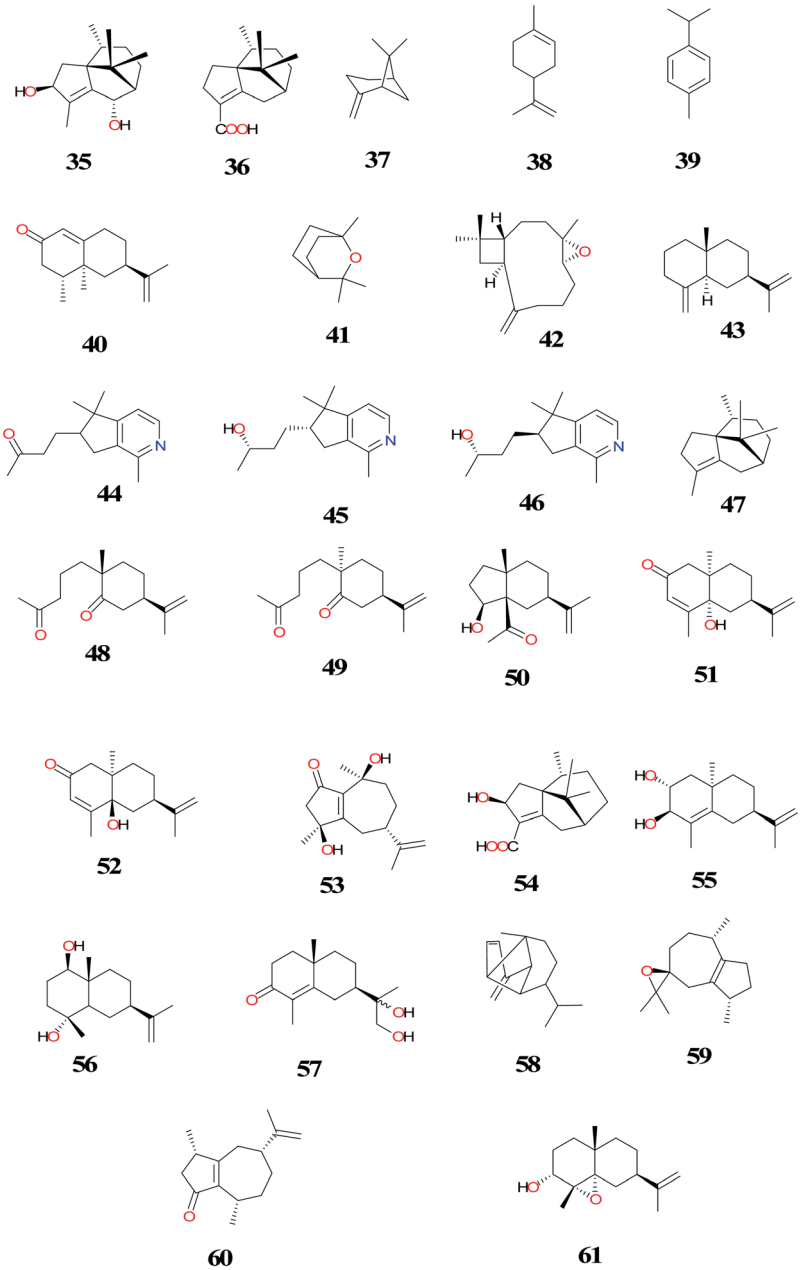


Fig. 4 Structures of terpenoids isolated from *Cyperus rotundus* (35 to 61).

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**.[17] 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-penylcyclohexanone (**48**), 2β-(5-oxopentyl)-2β-methyl-5β-isopropenylcyclohexanone (**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. suhtilis* at a concentration of 0.5 mg per disk; the other compounds did not show notable activities.[82]

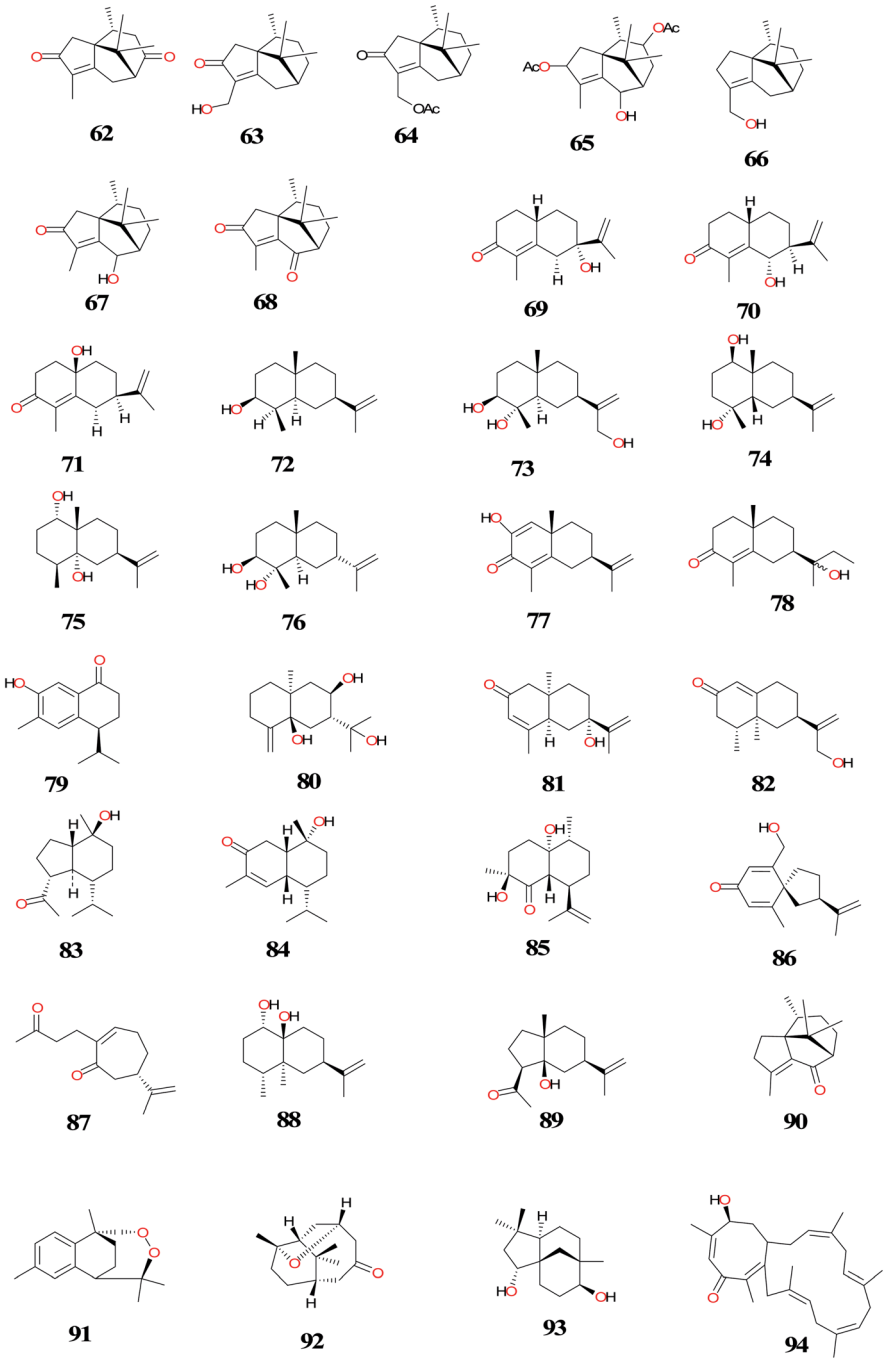


Fig. 5 Structures of terpenoids isolated from *Cyperus rotundus* (**62** to **94**).

The new sesquiterpenes, cyperusol A3 (**53**), 3β-hydroxycyperenoic 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-2*H*-tetrazolium bromide (MTT) assays and 11,12-dihydroxyeudesm-4-en-3-one (**57**) showed the most potent cytotoxic activity with observed IC_{50} values of 11.06 and 6.46 mm, respectively.[12]

Jin *et al.*[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-

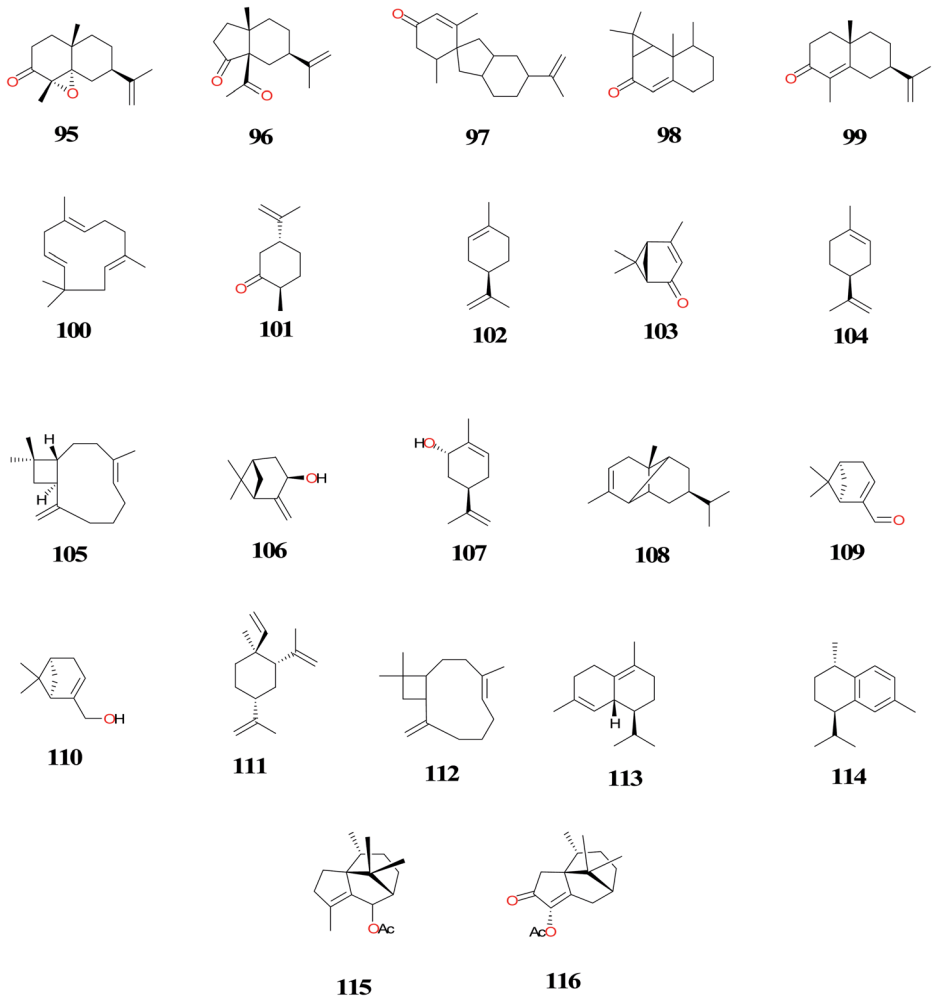


Fig. 6 Structures of terpenoids isolated from *Cyperus rotundus* (95 to 116).

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}.[11]

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-3α-ol (**61**).[79,124–127]

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.[13] The compounds include, five new patchoulane-type sesquiterpenoids, 3β-hydroxycyperenoic acid (**54**), cyperene-3,8-dione (**62**), 14-hydroxycyperotundone (**63**), 14-acetoxycyperotundone (**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 IC50 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.[13]

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

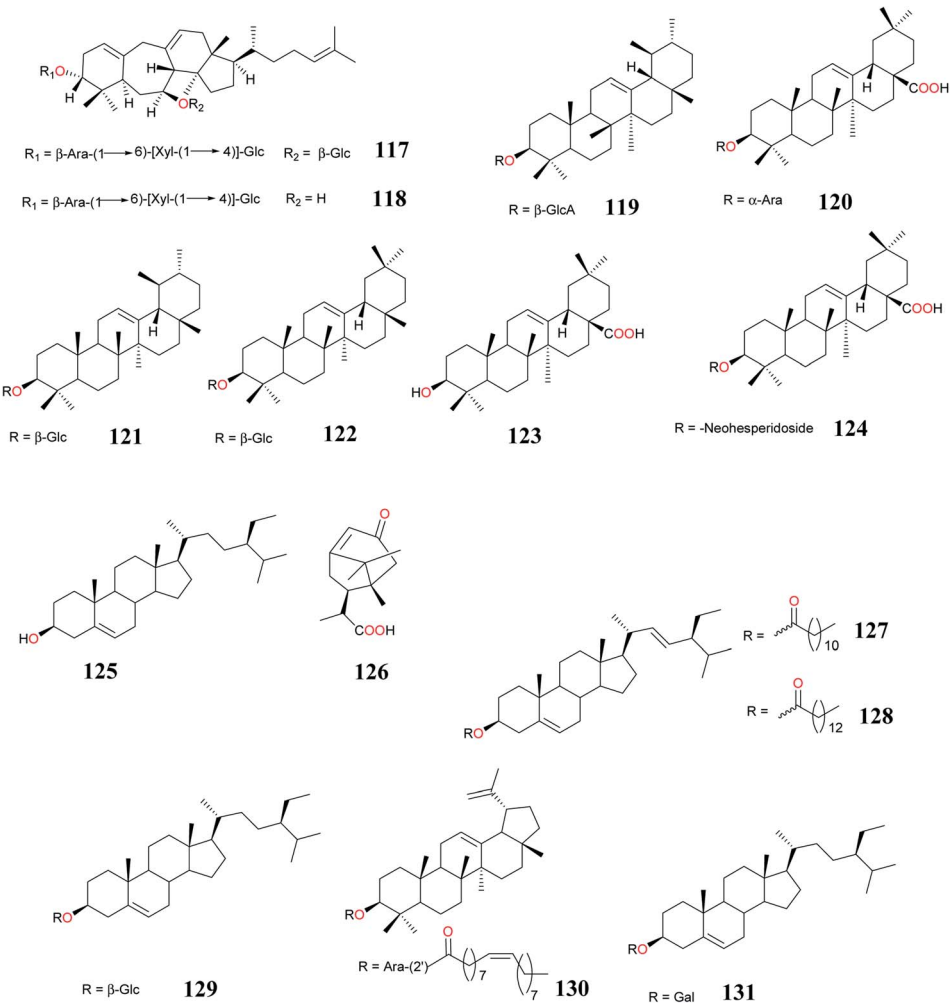


Fig. 7 Structures of terpenoids isolated from *Cyperus rotundus* (**117** to **131**).

90 and **91** were in the order of 10^{-4} M (1.08×10^{-4} and 3.45×10^{-4} M respectively).[81]

Chemical investigation of the rhizomes of CR led to the isolation of a new norsesquiterpenes, named norcyperone (**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.[84]

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.[93]

The new sesquiterpenes, 4α,5α-oxidoeudesm-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.[94] Compounds **4** and **17** isolated from the tubers of CR have showed growth inhibitory effects to both shoots and roots on the lettuce seedlings.[128]

Rani *et al.*[87] 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.[87]

Bioassay-guided fractionation of the methanol extracts of the rhizomes of CR led to the isolation of **41**, **42**, zerumbone (**99**), α-

Table 1 Summary of the bioactivity of derived terpenoids from *Cyperus rotundus*[a]

Compounds	Part (s)/place of harvest of plant studied (VS≠)	Measured activity	References
Rotundene (**1**)	NM/China	ND	Paknikar *et al.*,[120]
1, (−)-cypera-2,4-diene (**2**), cyprotene (**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**)	NM/gift of K.-D. Protzen, Paul Kadersd GmbH, Hamburg (NM)	ND	Sonwa *et al.*,[83]
3,4-*O*-isopropylideneshikimic acid (**22**), rotundusolide A (**23**), rotundusolide B (**24**), dehydrocostuslactone (**25**), (+)-alismoxide (**26**), sugetriol triacetate (**27**), 2β-hydroxy-α-cyperone (**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.*,[89]
4, **27**, *Epi*-guaidiol A (**33**), guaidiol A (**34**), sugebiol (**35**) and cyperenoic acid (**36**)	Rhizomes/Da-Bie-Shan Mountains, Anhui province, China. (No: 20060825)	ND	Xu *et al.*,[85]
10, **17**, β-pinene (**37**), limonene (**38**), 4-cymene (**39**), (+)-nootkatone (**40**), 1, 8-cineole (**41**), caryophyllene oxide (**42**), β-selinene (**43**)	Rhizomes/Purchased from Kyung Dong market place in Seoul, South Korea. (DKH-02561)	Anti-inflammatory activity	Tsoyi *et al.*,[17]
10,**17**, **37- 43**	Rhizomes/NM	Antiplatelet effects	Seo *et al.*,[77]
18	Rhizomes/Kyung Dong Crude Drugs Market, Seoul, South Korea. (CYRO1-2011)	Anti-inflammatory activity	Seo *et al.*,[123]
17	Rhizomes/Kyung Dong Crude Drugs Market, Seoul, South Korea. (CYRO1-2011)	Anti-inflammatory activity	Jung *et al.*,[121]
Rotundine A (**44**), rotundine B (**45**), and rotundine C (**46**)	Rhizomes/Purchased from Uchida Wakanyaku Co., Ltd. (Tokyo, Japan) (lot. 242 118)	ND	Jeong *et al.*,[15]
α-Cyperene (**47**)	NM/China (NM)	ND	Komai *et al.*,[80]
17, **19**, **40**, 2α-(5-oxopentyl)-2β-methyl-5β-isopropenylcyclohexanone (**48**), 2β-(5-oxopentyl)-2β-methyl-5β-isopropenylcyclohexanone (**49**), cyperolone (**50**), α-rutunol (**51**) and β-rutunol (**52**)	Roots/Yorishima, Okayama, Japan	Antibacterial activity	Ohira *et al.*,[82]
Cyperusol A_3 (**53**), 3β-hydroxycyperenoic acid (**54**), britanlin E (**55**), 1β, 4α-dihydroxyeudesm-11-ene (**56**) and 11,12-dihydroxyeudesm-4-en-3-one (**57**).	Rhizomes/Kyung Dong Crude Drugs Market, Seoul, South Korea. (CYRO1–2011)	Antitumor activity	Ryu *et al.*,[12]
10, **37–42**	Rhizomes/Kyung Dong Crude Drugs Market, Seoul, South Korea. (NM)	Anti-allergic activity	Jin *et al.*,[10]
Copadiene (**58**), epoxyguaien (**59**), and rotundone (**60**)	NM/Japan (NM)	ND	Kapadia *et al.*,[79]
19	NM/India (NM)	ND	Kapadia *et al.*,[124]
50	Rhizomes/Japan (NM)	ND	Hikino *et al.*,[125]
4α,5β-oxidoeudesm-11-*en*-3α-ol (**61**)	Rhizomes/Japan (NM)	ND	Hikino *et al.*,[127]
51 and **52**	Rhizomes	ND	Hikino *et al.*,[126]
4, **17**, **20**, **27**, **36**, **51**, **54**, cyperene-3,8-dione (**62**), 14-hydroxycyperotundone (**63**), 14-acetoxycyperotundone (**64**), sugetriol-3,9-diacetate (**65**), cyperenol (**66**), sugeonol (**67**), scariodione (**68**), (4a*S*, 7*S*)-7-hydroxy-1,4a-dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**69**), (4a*S*, 7*S*, 8R)-8-hydroxy-1,4a-dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7, 8-hexahydronaphtha-len-2(3*H*)-one (**70**), 1β-hydroxy-α-cyperone (**71**), 10-epieudesm-11-ene-3β, 5α-diol (**72**), 3β-hydroxyilicic alcohol (11(13)-eudesmene-3,4,12-triol) (**73**), cyperusol C (**74**), α-corymbolol (**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-calamenenone (**79**), rhombitriol (**80**), 7-*epi*-teucrenone (**81**), 12-hydroxynootkatone (**82**),	Rhizomes/Purchased from Juhuacun (Kunming, China) (no. 2011041101)	Anti-hepatitis B virus activity	Xu *et al.*,[13]

Table 1 (*Contd.*)

Compounds	Part (s)/place of harvest of plant studied (VS≠)	Measured activity	References
oplopanone (**83**), 10-hydroxyamorph-4-*en*-3-one (**84**), cyperusol D (**85**), argutosine D (**86**) and 4,5-seco-guaia-1 (10),11-diene-4,5-dioxo (**87**), oxyphyllol C (**88**) and 5-hydroxylucinone (**89**)			
42, patchoulenone (**90**) and 10,12-peroxycalamenene (**91**)	Tubers/Purchased from a Thai traditional dispensary, Bangkok, Thailand	Antimalarial activity	Thebtaranonth *et al.*,[81]
Norcyperone (**92**) and (−)-clovane-2,9-diol (**93**)	Rhizomes/Dabieshan Mountains of Anhui Province, P.R. China (no: 20060825)	ND	Xu *et al.*,[84]
27 and cyperalin A (**94**)	Rhizomes/King Abdulaziz University campus, Jeddah, Saudi Arabia (2014-CR110)	Anti-inflammatory activity	Ibrahim *et al.*,[93]
4, **17**, **18**, **47**, 4α,5α-oxidoeudesm-11-*en*-3-one (**95**) and cyper-11-ene-3,4-dione (**96**)	Rhizomes/purchased from Kyungdong-Yakryongsi traditional medicine market in Seoul, Korea (SKKU-PH-12-50)	Estrogenic activity	Park *et al.*,[94]
40, solavetivone (**97**) and aristolone (**98**)	Rhizomes/obtained from a registered medicinal plant vendor in Trivandrum (no. 034/2011)	Antioxidant activity	Rani *et al.*,[87]
17	Tubers/Bogor-Indonesia/NM	Insecticidal activity	Dadang *et al.*,[122]
41, **42**, zerumbone (**99**), α-humulene (**100**), (+)-dihydrocarvone (**101**), (*R*)-(+)-limonene (**102**), (1*S*)-(−)-verbenone (**103**), (*S*)-(−)-limonene (**104**), β-caryophyllene (**105**), (−)-(*E*)-pinocarveol (**106**), (*E*)-carveol (**107**), (−)-α-copaene (**108**), (1*R*)-(−)-myrtenal (**109**) and (1*R*)-(−)-myrtenol (**110**)	Rhizomes/Purchased from the Boeun medicinal herb shop (Seoul Yangnyeongsi, Seoul, South Korea) (CR-01)	Repellent activity	Chang *et al.*,[92]
4 and **17**	Rhizomes/supplied by Morihiro Kinoshita (Nihon Funmatsu Yakuhin Company, Japan) (NM)	Phytotoxicity	Morimoto *et al.*,[128]
4, **17**, **20**, **43**, **47**, **101**, 109, β-elemene (**111**), caryophyllene (**112**), δ-cadinene (**113**), calamenene (**114**), patchoulenyl acetate (**115**) and 6-acetoxy-patchoul-4-en-3-one (**116**)	Tubers/Islands of Oahu, Maui, Kauai and Hawaii (NM)	ND	Komai *et al.*,[80]
Cyprotuside A (**117**) and cyprotuside B (**118**)	Rhizomes/Zhanjiang, Guangdong Province of China (No.20090903)	Antidepressant activity	Zhou *et al.*,[90]
18-*Epi*-α-amyrin glucuronoside (**119**), oleanolic acid arabinoside (**120**), α-amyrin glucopyranoside (**121**) and β-amyrin glucopyranoside (**122**)	Tubers/West Champaran, Bihar, India (no. NISCAIR/RHMD/Consult/-2008-09/1114/145)	ND	Alam *et al.*,[86]
Oleanolic acid (**123**), oleanolic acid-3-*O*-neohesperidoside (**124**) and β-sitosterol (**125**)	Tubers/University of Allahabad campus, Allahabad, India (NM)	ND	Singh *et al.*,[114]
12-Methyl cyprot-3-en-2-one-13-oic acid (**126**), stigmasterol-*n*-dodecanoate (**127**), stigmasterol-*n*-tetradecanoate (**128**), β-sitosterol glucoside (**129**) and lupenyl arabinopyranosyl oleate (**130**)	Tubers/Purchased from a Delhi market	ND	Sultana *et al.*,[91]
Sitosteryl (**131**)	Aerial parts/El-Safa and El-Marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt.	Antifeedant and Cytotoxic activity	Sayed *et al.*,[33]

[a] VS≠: Voucher specimen number, NM: not mention, ND: not done.

humulene (**100**), (+)-dihydrocarvone (**101**), (*R*)-(+)-limonene (**102**), (1*S*)-(−)-verbenone (**103**), (*S*)-(−)-limonene (104), β-caryophyllene (105), (−)-(*E*)-pinocarveol (**106**), (*E*)-carveol (**107**), (−)-α-copaene (**108**), (1*R*)-(−)-myrtenal (**109**) and (1*R*)-(−)-myrtenol (**110**). The compounds were tested for repellency to male *Blattella germanica* and the results were compared to *N*,*N*-diethyl-3-methylbenzamide (deet). In filter-paper choice tests, **99** was the most repellent compound, and **100** was ineffective, which shows that α,β-unsaturated carbonyl group of **99** contributes to repellency. The article reported that at 81.5 μg

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 aureusidin (**134**)	Leaves/stem, Australia (K. L. Wilson 3309) (Denistone, N.S.W)	ND	Harborne *et al.*,[141]
Afzelechin (**135**), (+)-catechin (**136**), luteolin (**137**), and quercetin (**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**), oreintin (**145**), epiorientin (**146**), myricetin-3-*O*-β-D-galactopyranoside (**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-*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.

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**), caryophyllene (**112**), δ-cadinene (**113**), calamenene (**114**), petchoulenyl 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.[80]

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**).[86]

The sesquiterpenoid, 12-methyl cyprot-3-en-2-one-13-oic acid (**126**), steroidal esters; stigmasterol-*n*-dodecanoate (**127**), stigmasterol-*n*-tetradecanoate (**128**), β-sitosterol glucoside (**129**) and triterpenoid glycosides; lupenyl arabinopyranosyl oleate (**130**) were isolated for the first time and they could serve as chromatographic markers for standardization of the tubers of CR.[91] A new steroid glycoside; sitosteryl (**131**) and other compounds were also isolated from the aerial parts of this plant species harvested in Egypt.[33]

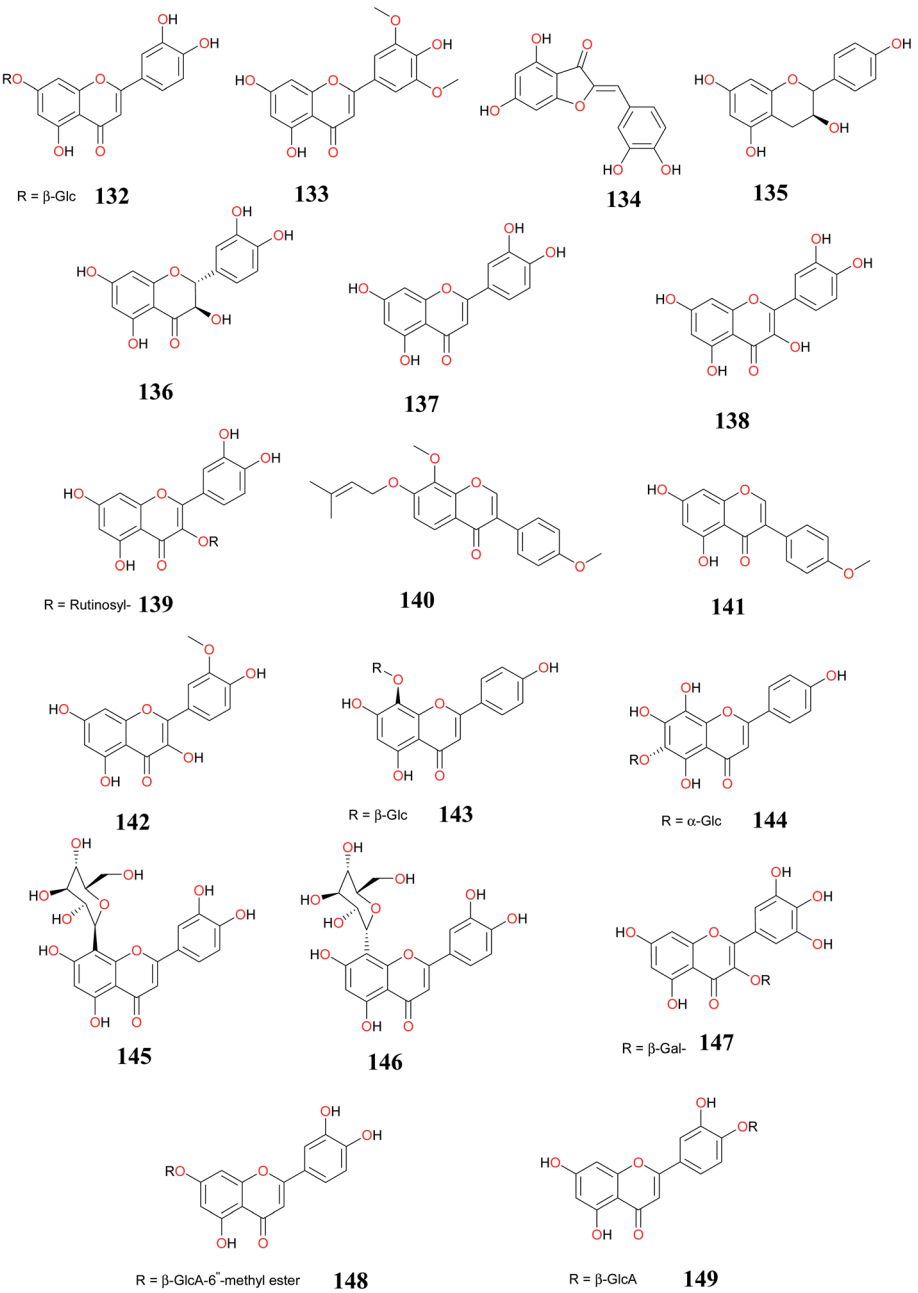


Fig. 8 Structures of flavonoids isolated from *Cyperus rotundus* (132 to 149).

3.2 Flavonoids

Flavonoids continue to attract attention as potentially useful compounds because of their broad spectrum of biological activities.[129–140] 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.*[141] 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 (IC_{50} = 25 g mL^{-1}) and protecting against H_2O_2/UV-photolysis induced DNA damage.[40] Rutin (**139**), pongamone A (**140**) and biochanin A (**141**) were

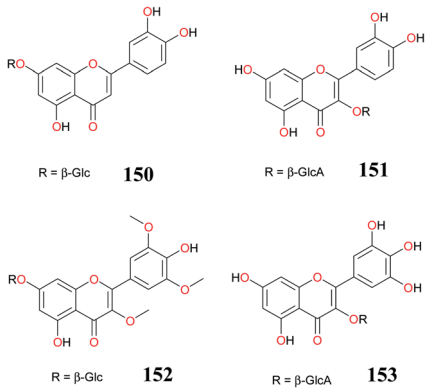


Fig. 9 Structures of flavonoids isolated from *Cyperus rotundus* (150 to 153).

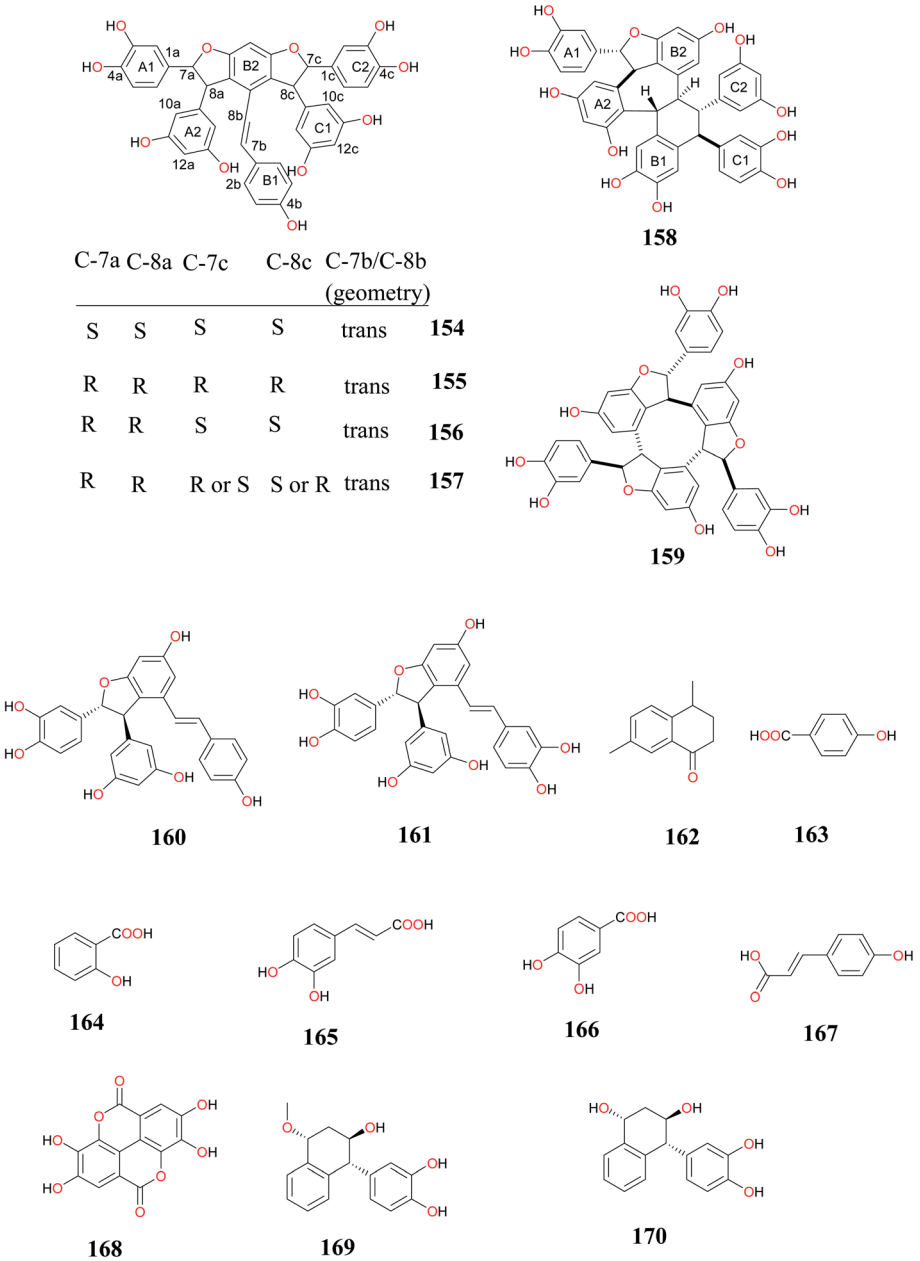
isolated from the rhizomes of this plant species and the structure was established on the basis of 1D and 2D NMR spectroscopic analyses.[11,78] Luteolin (**137**) has been isolated from the rhizomes of this plant species.[18]

Chemical investigation of the aerial parts of CR led to the isolation **133**, isorhamnetin (**142**), vitexin (**143**), isovitexin (**144**), oreintin (**145**), epiorientin (**146**), myricetin-3-*O*-β-D-galactopyranoside (**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**). Compounds (**146–148**) having an *ortho*-dihydroxyl groups at ring B showed strong antioxidant activity. The presence of a hydroxyl group at position-3 increased the antioxidant activity in **143**. Compounds (**133**, **143**, **144**, **146**, **148**) demonstrated strong α-amylase inhibitory activity > 50% influenced by the presence of free hydroxyl groups at 7, 3′ and 4′ positions.[8,33] The flavonoids **144**, **146**, cinaroside (**150**), quercetin-*O*-β-D-glucuronopyranoside (**151**), cyperaflavoside (**152**) and myricetin-3-*O*-β-D-glucuronopyranoside (**153**) were also isolated from the aerial parts and screened for their 5-lipoxygenase inhibitory potential. All compounds demonstrated 5-lipoxygenase inhibitory potentials with IC_{50}s 5.1 (**152**), 4.5 (**143**), 5.9 (**145**), 4.0 (**150**), 3.7 (**151**), and 2.3 μM (**153**), respectively, in comparison to indomethacin (IC_{50} = 0.98 M).[93]

Table 3 Summary of the bioactivity of derived stilbenes and derivatives from *Cyperus rotundus*[a]

Compounds	Part (s)/place of harvest of plant studied (VS≠)	Measured activity	References
(+)-Cyperusphenol A (**154**), (−)-(*E*)-cyperusphenol A (**155**), (*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.*,[18]
4,7-Dimethyl-1-tetralone (**162**)	Tubers/Purchased from a Thai traditional dispensary, Bangkok, Thailand	Antimalarial activity	Thebtaranonth *et al.*,[81]
p-Hydroxybenzoic acid (**163**)	Rhizomes/Purchased from Uchida Wakanyaku Co., Ltd. (Tokyo, Japan) (lot. 242118)	ND	Jeong *et al.*,[15]
Salicylic acid (**164**), caffeic acid (**165**), protocatechuic acid (**166**) and *p*-coumaric acid (**167**)	Aerial parts/El-Safa and El-marwa, Faculty of Agriculture, Al-Azhar University, Assiut, Egypt	Antifeedant and Cytotoxic activity	Sayed *et al.*,[33]
167, and ellagic acid (**168**)	Rhizomes/Purchased from Kyung Dong market place in Seoul, South Korea. (DKH-02561)	Anti-inflammatory activity	Tsoyi *et al.*,[17]
164–167, methoxycyperotundol (**169**) and cyperotundol (**170**)	Rhizomes/Collected in Zhanjiang, Guangdong Province of China (no. 20090903)	ND	Zhou *et al.*,[11]
Galloylquinic 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.*,[40]
Chlorogenic acid (**174**)	Rhizomes/obtained as Organic Musta Powder (Khandige Organic Health Product, Bangalore, India) (NM)	Anti-inflammatory activity	Rocha *et al.*,[10]
Methyl-3,4-dihydroxybenzoate (**175**)	Rhizomes/Al-Azhar University campus, Assiut Branch, Egypt (2009-CR110)	Hepatoprotective activity	Mohamed,[78]

[a] VS≠: Voucher specimen number, NM: not mention, ND: not done.



C-7a	C-8a	C-7c	C-8c	C-7b/C-8b (geometry)	
S	S	S	S	trans	154
R	R	R	R	trans	155
R	R	S	S	trans	156
R	R	R or S	S or R	trans	157

Fig. 10 Structures of stilbenes, ellagic acid derivatives and other compounds from *Cyperus rotundus* (**154** to **170**).

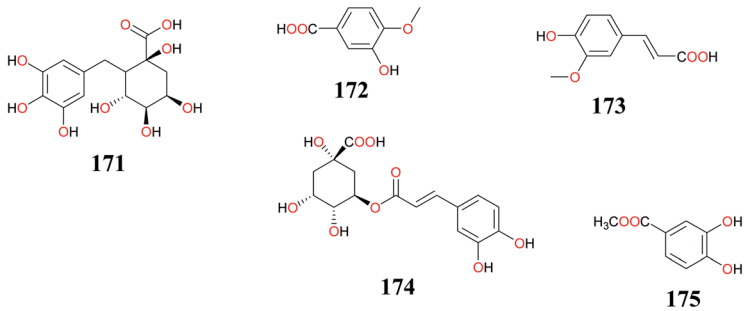


Fig. 11 Structures of stilbenes and derivativesisolated from *Cyperus rotundus* (**171** to **175**).

Table 4 Miscellaneous compounds from *Cyperus* rotundus[a]

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

[a] VS≠: Voucher specimen number, NM: Not mention, ND: Not done.

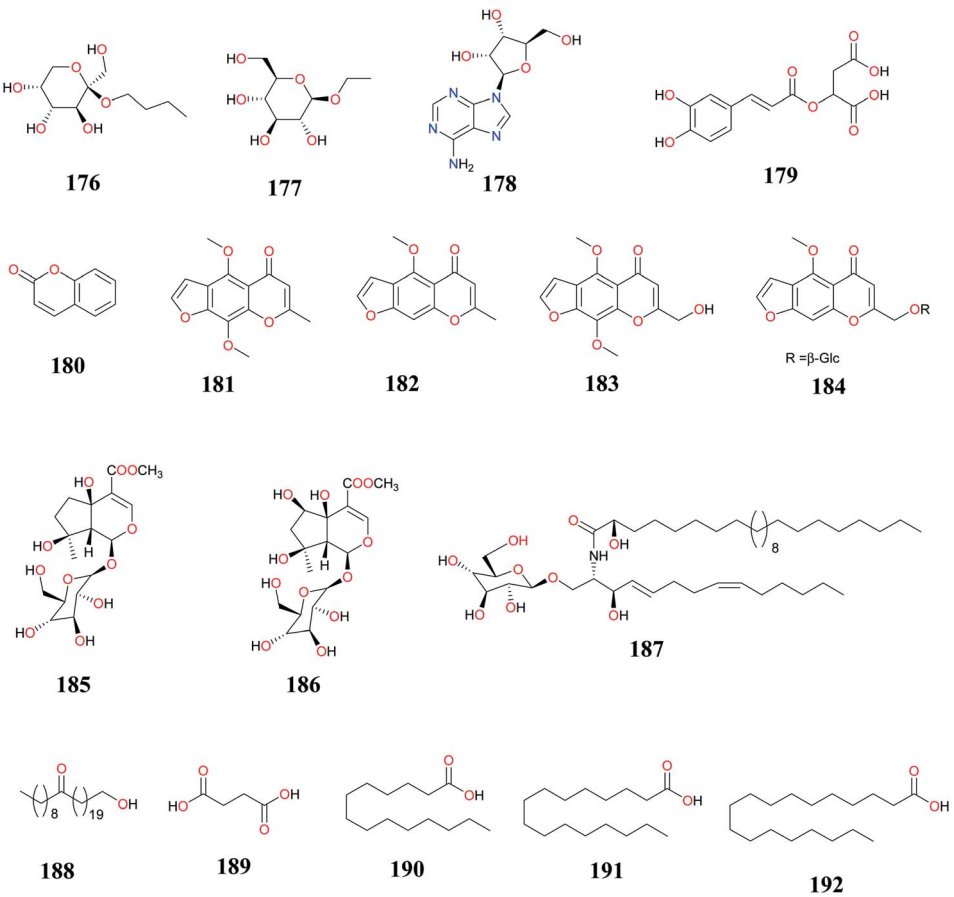


Fig. 12 Structures of miscellaneous compoundsisolated from *Cyperus rotundus* (**176** to **192**).

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.[142] The stilbenes and derivates (**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 IC_{50} 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.[18] Salicylic acid (**164**), caffeic acid (**165**), protocatechuic acid (**166**) and *p*-coumaric acid (**167**) isolated from this weed showed significant antioxidant activity.[8] 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.[33]

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 anti-feedant activities.[8,33] 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-proliferation, and growth inhibitory properties respectively.[78,86,143,144]

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 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.

Acknowledgements

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References

1 R. Sharma and R. Gupta, *Life Sci.*, 2007, **80**, 2389–2392.
2 K. H. Kumar, S. Razack, I. Nallamuthu and F. Khanum, *Ind. Crops Prod.*, 2014, **52**, 815–826.
3 S. B. Badgujar and A. H. Bandivdekar, *J. Ethnopharmacol.*, 2015, **163**, 39–42.
4 A. Stierle, R. Upadhyay and G. Strobel, *Phytochemistry*, 1991, **30**, 2191–2192.
5 Y. Jaiswal, Z. Liang, P. Guo, H. M. Ho, H. Chen and Z. Zhao, *J. Agric. Food Chem.*, 2014, **62**, 7302–7316.
6 T. K. Lim, *Cyperus rotundus. Edible medicinal and non-medicinal plants*, Springer Science + Business Media Dordrecht, 2016, vol. 10, pp.178–208.
7 W. G. Seo, H. O. Pae, G. S. Oh, K. Y. Chai, T. O. Kwon, Y. G. Yun, N. Y. Kim and H. T. Chung, *J. Ethnopharmacol.*, 2001, **76**, 59–64.
8 H. M. Sayed, M. H. Mohamed, S. F. Farag, G. A. Mohamed, O. R. M. Omobuwajo and P. Proksch, *Nat. Prod. Res.*, 2008, **22**, 1487–1497.
9 M. Kumar, M. Rani and B. Meher, *Curr. Res. Pharm. Sci.*, 2017, **07**, 11–15.

10 J. H. Jin, D. U. Lee, Y. S. Kim and H. P. Kim, *Arch. Pharm. Res.*, 2011, **34**, 223–228.
11 Z. Zhou and W. Yin, *Molecules*, 2012, **17**, 12636–12641.
12 B. Ryu, H. M. Kim, J. S. Lee, Y. J. Cho, M. S. Oh, J. H. Choi and D. S. Jang, *HeIv. Chim. Acta*, 2015, **98**, 1372–1379.
13 H. B. Xu, Y. B. Ma, X. Y. Huang, C. A. Geng, H. Wang, Y. Zhao, T. H. Yang, X. L. Chen, C. Y. Yang, X. M. Zhang and J. J. Chen, *J. Ethnopharmacol.*, 2015, **171**, 131–140.
14 N. A. Raut and N. J. Gaikwad, *Fitoterapia*, 2006, **77**, 585–588.
15 S. J. Jeong, T. Miyamoto, M. Inagaki, Y. C. Kim and R. Higuchi, *J. Nat. Prod.*, 2000, **63**, 673–675.
16 J. H. Nam, D. Y. Nam and D. U. Lee, *J. Nat. Prod.*, 2016, **79**, 1091–1096.
17 K. Tsoyi, H. J. Jang, Y. S. Lee, Y. M. Kim, H. J. Kim, H. G. Seo, J. H. Lee, J. H. Kwak, D. U. Lee and K. C. Chang, *J. Ethnopharmacol.*, 2011, **137**, 1311–1317.
18 T. Ito, H. Endo, H. Shinohara, M. Oyama, Y. Akao and M. Iinuma, *Fitoterapia*, 2012, **83**, 1420–1429.
19 L. Boulos and M. N. El-Hadidi, *The weed flora of Egypt*, The American University in Cairo Press, Cairo, 1984, p. 58.
20 N. Singh, V. K. Kulshrestha, M. B. Gupta and K. P. Bhargava, *Indian J. Med. Res.*, 1970, **58**, 103–109.
21 M. B. Gupta, T. K. Palit, N. Singh and K. P. Bhargava, *Indian J. Med. Res.*, 1971, **59**, 76–82.
22 K. Komai and K. Ueki, *Weed Res. Japan*, 1980, **25**, 42–47.
23 K. Komai, C. S. Tang and R. K. Nishimoto, *J. Chem. Ecol.*, 1991, **17**, 1–8.
24 P. Kalsi, A. Sharma, A. Singh, I. P. Singh and B. R. Chhabra, *Fitoterapia*, 1995, **66**, 94.
25 M. Zhu, H. H. Luk, H. S. Fung and C. T. Luk, *Phytother. Res.*, 1997, **11**, 392–395.
26 S. C. Umeric and H. O. Ezeuzo, *Bioresour. Technol.*, 2000, **72**, 193–196.
27 J. H. Ha, K. Y. Lee, H. C. Choi, J. Cho, B. S. Kang, J. C. Lim and D. U. Lee, *Biol. Pharm. Bull.*, 2002, **25**, 128–130.
28 M. Zhu, H. H. Luk, H. S. Fung and C. T. Luk, *Phytother. Res.*, 1998, **11**, 392–394.
29 S. J. Uddin, K. Mondal, J. A. Shilpi and M. T. Rahman, *Fitoterapia*, 2006, **77**, 134–136.
30 D. K. Pal and S. Dutta, *Indian J. Pahrm. Sci.*, 2006, **68**, 256–258.
31 A. Puratchikody, C. N. Devi and G. Nagalakshmi, *Indian J. Pharm. Sci.*, 2006, **68**, 97–101.
32 B. Lemaure, A. Touché, I. Zbinden, J. Moulin, D. Courtois, K. Macé and C. Darimont, *Phytother. Res.*, 2007, **21**, 724–730.
33 H. M. Sayed, M. H. Mohamed, S. F. Farag, G. A. Mohamed and P. Proksch, *Nat. Prod. Res.*, 2007, **21**, 343–350.
34 A. Ardestani and R. Yazdanparast, *Int. J. Biol. Macromol.*, 2007, **41**, 572–578.
35 Z. A. Nima, M. S. Jabier, R. I. Wagi and H. A. Hussain, *Eng. Technol.*, 2008, **26**, 1156–1159.
36 V. Kempraj and S. K. Bhat, *Nat. Prod. Radiance*, 2008, **7**, 416–419.
37 M. S. Sundaram, T. Sivakumar and G. Balamurugan, *Biomedicine*, 2008, **28**, 302–304.
38 S. I. Shivakumar, H. M. Suresh, C. S. Hallikeri, B. C. Hatapakki, J. S. Handiganur, K. Sankh and B. Shivakumar, *J. Nat. Remed.*, 2009, **9**, 92–196.
39 F. Mojab, H. Vahidi, B. Nickavar and M. Kamali-Nejad, *J. Med. Plant*, 2009, **8**, 91–97.
40 S. Kilani-Jaziri, A. Neffati, I. Limem, J. Boubaker, I. Skandrani, M. B. Sghair, I. Bouhlel, W. Bhouri, A. M. Mariotte, K. Ghedira, M. G. Dijoux-Franca and L. Chekir-Ghedira, *Chem. Biol. Interact.*, 2009, **181**, 85–94.
41 D. Pal, S. Dutta and A. Sarkar, *Acta Pol. Pharm.*, 2009, **66**, 535–541.
42 M. E. Güldür, A. Ozgónül, I. H. Kilic, O. Sögüt, M. Ozaslan, M. Bitiren, M. Yalcin and D. Musa, *Int. J. Pharmacol.*, 2010, **6**, 104–110.
43 A. Bisht, G. R. S. Bisht, M. Singh, R. Gupta and V. Singh, *Int. J. Res. Pharm. Biomed. Sci.*, 2011, **2**, 661–665.
44 A. Singh, S. Maurya, R. Singh and U. P. Singh, *Arch. Phytopathol. Plant Prot.*, 2011, **44**, 2004–2011.
45 A. G. Sunil, K. S. Kesavanarayanan, P. Kalaivani, S. Sathiya, V. Ranju, R. J. Priya, B. Pramila, F. D. S. Paul, J. Venkhatesh and C. S. Babu, *Brain Res. Bull.*, 2011, **84**, 394–405.
46 P. G. Daswani, S. Brijesh, P. Tetali and T. J. Birdi, *Indian J. Pharmacol.*, 2011, **43**, 340–344.
47 G. K. Dang, R. R. Parekar, S. K. Kamat, A. M. Scindia and N. N. Rege, *Phytother. Res.*, 2011, **25**, 904–908.
48 S. M. Khan and D. U. Lee, *Nat. Prod. Sci.*, 2011, **17**, 250–255.
49 M. Khalili, Z. Kiasalari, M. Roghani and Y. Azizi, *J. Med. Plant. Res.*, 2011, **5**, 1140–1146.
50 N. Singh, B. R. Pandey, P. Verma, M. Bhalla and M. Gilca, *Indian J. Nat. Prod. Res.*, 2012, **3**, 467–476.
51 D. Jebasingh, S. Venkataraman, D. D. Jackson and B. S. Emerald, *Int. J. Appl. Res. Nat. Prod.*, 2012, **5**, 1–8.
52 G. F. A. El-Kaream, *J. Intercult. Ethnopharmacol.*, 2012, **1**, 111–118.
53 R. S. Chandratre, S. Chandarana and S. A. Mengi, *Int. J. Pharm. Biol. Arch.*, 2012, **3**, 598–600.
54 A. Chithran, B. T. Ramesh and N. Himaja, *Int. J. Phytopharmacol.*, 2012, **3**, 130–134.
55 K. H. Kumar and F. Khanum, *Cell Mol. Neurobiol.*, 2013, **33**, 5–17.
56 H. Weenen, M. H. H. Nkunya, D. H. Bray, L. B. Mwasumbi, L. S. Kinabo, V. A. E. B. Kilimali and J. B. P. A. Wijnberg, *Planta Med.*, 1990, **56**, 371.
57 M. Ahmad, M. Mahayrookh, B. R. Asif and N. Jahan, *Pak. J. Pharmacol.*, 2012, **29**, 7–13.
58 K. H. Kumar and F. Khanum, *Cell Mol. Neurobio.*, 2013, **33**, 5–17.
59 S. Krishna and S. Renu, *J. Drug Del. Ther.*, 2013, **3**, 109–113.
60 K. H. Kumar, A. Tamatam, A. Pal and F. Khanum, *Neurotoxicol*, 2013, **34**, 150–159.
61 Z. Rabiei, M. Hojjati, M. Rafieian-Kopaeia and Z. Alibabaei, *Biomed. Aging Pathol.*, 2013, **3**, 185–191.
62 H. Imam, Z. Riaz and G. Sofi G, *Int. J. Green Pharm.*, 2013, **7**, 37–40.
63 G. F. Mohammed, *Aesthet. Surg. J.*, 2014, **34**, 298–305.

64 S. E. Park, W. T. Shin, C. Park, S. H. Hong, G. Y. Kim, S. O. Kim, C. H. Ryu, S. H. Hong and Y. H. Choi, *Oncol. Rep.*, 2014, **32**, 2461–2470.
65 D. Jebasingh, D. D. Jackson, S. Venkataraman, E. Adeghate and B. S. Emerald, *Pharm. Biol.*, 2014, **15**, 1–12.
66 M. Z. Imam and C. D. Sumi, *BMC Complement. Altern. Med.*, 2014, **14**, 83.
67 H. Imam, S. Zarnigar, A. Ghulamuddin and L. A. Seikh, *Int. J. Nutr. Pharmacol. Nuerol. Dis.*, 2014, **4**, 23–27.
68 H. H. T. Tran, M. C. Nguyen, H. T. Le, T. L. Nguyen, T. B. Pham and V. M. Chau, *J. Pharm. Biol.*, 2014, **52**, 74–77.
69 K. Athesh, M. Divakar and P. Brindha, *Asian J. Pharm. Clin. Res.*, 2014, **7**, 88–92.
70 A. M. Peerzada, H. H. Ali, M. Naeem, M. Latif, A. H. Bukhari and A. Tanveer, *J. Ethnopharmacol.*, 2015, **174**, 540–560.
71 S. Kasala, K. Ramanjaneyulu, J. Himabindhu, R. Alluri and R. R. Babu, *J. Pharmacogn. Phytochem.*, 2016, **5**, 407–409.
72 S. Suryavanshi, A. Choudhari, P. Raina and R. Kaul-Ghanekar, *J. Ethnopharmacol.*, 2019, **242**, 10.
73 F. Wang, X. Song, S. Ma, C. Liu, X. Sun, X. Wang, Z. Liu, D. Liang and Z. Yu, *Biosci. Rep.*, 2019, **39**, BSR20190502.
74 S. Ma, F. Wang, C. Zhang, X. Wang, X. Wang and Z. Yu, *BMC Complementary Med. Therapies*, 2020, **20**, 262.
75 Z. Shakerin, E. Esfandiari, S. Razavi, H. Alaei, M. Ghanadian and G. Dashti, *Adv. Biomed. Res.*, 2020, **9**, 17.
76 R. S. Dhillon, S. Singh, S. Kundra and A. S. Basra, *Plant Growth Regul.*, 1993, **13**, 89–93.
77 E. J. Seo, D. J. Lee, J. H. Kwak, S. M. Lee, Y. S. Kim and Y. S. Jung, *J. Ethnopharmacol.*, 2011, **135**, 48–54.
78 G. A. Mohamed, *Bull. Fac. Pharm. Cairo Univ.*, 2015, **53**, 5–9.
79 V. H. Kapadia, V. G. Naik, M. S. Wadia and S. Dev, *Tetrahedron Lett.*, 1967, **47**, 4661–4667.
80 K. Komai and C. S. Tang, *Phytochemistry*, 1989, **28**, 1883–1886.
81 C. Thebtaranonth, Y. Thebtaranonth, S. Wanauppathamkul and Y. Yuthavong, *Phytochemistry*, 1995, **40**, 125–128.
82 S. Ohira, T. Hasegawa, K. I. Hayashi, T. Hoshino, D. Takaoka and H. Nozaki, *Phytochemistry*, 1998, **47**, 1577–1581.
83 M. M. Sonwa and W. A. König, *Phytochemistry*, 2001, **58**, 799–810.
84 Y. Xu, H. W. Zhang, C. Y. Yu, Y. Lu, Y. Chang and Z. M. Zou, *Molecules*, 2008, **13**, 2474–2481.
85 Y. Xu, H. W. Zhang, X. C. Wan and Z. M. Zoua, *Magn. Reson. Chem.*, 2009, **47**, 527–531.
86 P. Alam, M. Ali and V. Aeri, *J. Nat. Prod. Plant Resour.*, 2012, **2**, 272–280.
87 M. P. Rani and K. P. Padmakumari, *J. Chromatogr. B*, 2012, **904**, 22–28.
88 G. F. Mohammed, *Aesthet. Surg. J.*, 2014, **34**, 298–305.
89 J. L. Yang and Y. P. Shi, *Planta Med.*, 2012, **78**, 59–64.
90 Z. L. Zhou, S. Q. Lin and W. Q. Yin, *J. Asian Nat. Prod. Res.*, 2016, **18**, 662–668.
91 S. Sultana, M. Ali and S. R. Mir, *Open Plant Sci. J.*, 2017, **10**, 82–91.
92 K. S. Chang, J. H. Jeon, G. H. Kim, G. W. Jang, S. J. Jeong, Y. R. Ju and Y. J. Ahn, *Sci. Rep.*, 2017, **7**, 16643.
93 S. R. M. Ibrahim, G. A. Mohamed, K. Z. Alshali, R. A. Al Haidari, A. A. El-Kholy and M. F. Zayed, *Braz. J. Pharmacog.*, 2018, **28**, 320–324.
94 Y. J. Park, H. Zheng, J. H. Kwak and K. H. Chung, *Biomed. Pharmacother.*, 2019, **109**, 1313–1318.
95 M. A. Gamal, K. M. K. Hani and I. R. M. Sabrin, *Int. J. Pharmacogn. Phytochem. Res.*, 2015, **7**, 83–99.
96 A. Kamala, S. K. Middha and C. S. Karigar, *3 Biotech*, 2018, **8**, 309.
97 L. Jirovetz, A. Wobus, G. Buchbauer, M. P. Shafi and P. T. Thampi, *Plant*, 2004, **7**, 100–106.
98 S. Kilani, A. Abdelwahed, I. Chraief, R. B. Ammar, N. Hayder, M. Hammami, K. Ghedira and L. Chekir-Ghedira, *J. Essent. Oil*, 2005, **17**, 695–700.
99 S. Kilani, I. Bouhlel, R. Ben, A. Abdelwahed, N. Hayder, A. Mahmoud, K. Ghedira and L. Chekir-Ghedira, *Toxicol. Environ. Chem.*, 2005, **87**, 415–425.
100 R. Yazdanparast and A. Ardestani, *J. Med. Food*, 2007, **10**, 667–674.
101 S. Kilani, S. M. Ben, I. Limem, I. Bouhlel, J. Boubaker, W. Bhouri, I. Skandrani, A. Neffatti, R. Ben-Ammar, M. G. Dijoux-Franca, K. Ghedira and L. Chekir-Ghedira, *Bioresour. Technol.*, 2008, **99**, 9004–9008.
102 S. Kilani, J. Ledauphin, I. Bouhlel, M. Ben-Sghaier, J. Boubaker, I. Skandrani, R. Mosrati, K. Ghedira, D. Barillier and L. Chekir-Ghedira, *Chem. Biodivers.*, 2008, **5**, 729–742.
103 O. A. Lawal and A. O. Oyedeji, *Molecules*, 2009, **14**, 2909–2917.
104 S. Kilani-Jaziri, W. Bhouri, I. Skandrani, I. Limem, L. Chekir-Ghedira and K. Ghedira, *S. Afr. J. Bot.*, 2011, **77**, 767–776.
105 S. Kilani-Jaziri, D. Mhalla, F. Châbane, Z. Ghedira, I. Limem, K. Ghedira and L. Chekir-Ghedira, *BMC Complement. Alternat. Med.*, 2013, **13**, 28.
106 A. Sharma, R. Verma and P. Ramteke, *J. Herbal Med.*, 2014, **4**, 74–82.
107 P. Mannarreddy, M. Denis, D. Munireddy, R. Pandurangan, K. P. Thangavelu and K. Venkatesan, *Biomed. Pharmacother.*, 2017, **95**, 1375–1387.
108 Q. P. Hu, X. M. Cao, D. L. Hao and L. L. Zhang, *Sci. Rep.*, 2017, **7**, 45231.
109 R. A. Abo-Altemen, A. M. Al-Shammari and M. S. Shawkat, *Energy Procedia*, 2019, **157**, 1462–1474.
110 F. G. Rocha, M. D. M. Brandenburg, P. L. Pawloski, B. D. S. Soley, S. C. A. Costa, C. C. Meinerz, I. P. Baretta, M. F. Otuki and D. A. Cabrini, *J. Ethnopharmacol.*, 2020, **254**, 112709.
111 B. Huang, J. Liu, S. Fu, Y. Zhang, Y. Li, D. He, X. Ran, X. Yan, J. Du, T. Meng, X. Gao and D. Liu, *Front. Pharmacol.*, 2020, **11**, 281.
112 K. Komai and K. Ueki K, *J. Weed Sci. Technol.*, 1975, **20**, 66–71.
113 K. Komai, J. Iwamura and K. Ueki, *J. Weed Sci. Technol.*, 1977, **22**, 14–18.
114 P. N. Singh and S. B. Singh, *Phytochemistry*, 1980, **19**, 2056.

115 S. K. Kim, B. Y. Hwang, S. J. Kang, J. J. Lee, J. S. Ro and K. Lee, *Koran J. Pharmacogn.*, 2000, **31**, 1–6.
116 S. J. Kim, H. J. Kim, Y. P. Jang, M. S. Oh and D. S. Jang, *Bull. Korean Chem.*, 2012, **33**, 3115–3118.
117 H. G. Kim, J. Hong, Y. Huh, C. Park, D. S. Hwang, J. H. Choi and M. S. Oh, *J. Ethnopharmacol.*, 2013, **148**, 322–328.
118 S. J. Kim, B. Ryu, H. Y. Kim, Y. I. Yang, J. Ham, J. H. Choi and D. S. Jang, *Bull. Korean Chem. Soc.*, 2013, **34**, 2207–2210.
119 Y. X. Li, *J. Chem. Pharm. Res.*, 2014, **6**, 1496–1500.
120 S. K. Paknikar, O. Motl and K. K. Chakravarti, *Tetrahedron Lett.*, 1977, **24**, 2121–2124.
121 S. H. Jung, S. J. Kim, B. G. Jun, K. T. Lee, S. P. Hong, M. S. Oha, D. S. Jang and J. H. Choi, *J. Ethnopharmacol.*, 2013, **147**, 208–214.
122 A. Dadang, K. Ohsawa, S. Kato and I. Yamamoto, *J. Pesticide Sci.*, 1996, **21**, 444–446.
123 Y. J. Seo, M. Jeong, K. T. Lee, D. S. Jang and J. H. Choi, *Int. Immunopharmacol.*, 2016, **38**, 61–69.
124 V. H. Kapadia, B. A. Nagasampagi, V. G. Naik and S. Dev, *Tetrahedron*, 1965, **21**, 607–618.
125 H. Hikino, K. Aota and T. Takemoto, *Tetrahedron*, 1967, **23**, 2169–2172.
126 H. Hikino, K. Aota, D. Kuwano and T. Takemoto, *Tetrahedron*, 1971, **27**, 4831–4836.
127 H. Hikino and K. Aota, *Phytochemistry*, 1976, **16**, 1265–1266.
128 M. Morimoto and K. Komai, *Weed Biol. Manage.*, 2005, **5**, 203–209.
129 S. Rune, F. Torgils and M. V. Ingunn, *J. Agric. Food Chem.*, 2007, **55**, 10067.
130 P. R. Jensen, K. M. Jenkins, D. Porter and W. Fenical, *Appl. Environ. Microbiol.*, 1998, **64**, 1490.
131 C. N. Liu, S. H. Kuo and M. C. Chung, *J. Nat. Prod.*, 1997, **60**, 851.
132 H. W. Chu, H. T. Wu and Y. J. Lee, *Tetrahedron*, 2004, **60**, 2647.
133 S. Li, C. Y. Lo and C. T. Ho, *J. Agric. Food Chem.*, 2006, **54**, 4176.
134 J. H. Yoon, T. G. Lim, K. M. Lee, A. J. Jeon, S. Y. Kim and K. W. Lee, *J. Agric. Food Chem.*, 2011, **59**, 222.
135 S. E. Nielsen, V. Breinholt, C. Cornett and L. O. Dragsted, *Food Chem. Toxicol.*, 2000, **38**, 739.
136 Z. Cheng, S. Surichan, K. Ruparelia, R. Arroo and M. R. Boarder, *Br. J. Pharmacol.*, 2011, **162**, 1781.
137 S. Li, M. H. Pan, C. S. Lai, C. Y. Lo, S. Dushenkov and C. T. Ho, *Bioorg. Med. Chem.*, 2007, **15**, 3381.
138 G. Casano, A. Dumetre, C. Pannecouque, S. Hutter, N. Azas and M. Robin, *Bioorg. Med. Chem.*, 2010, **18**, 6012.
139 N. Beldjoudi, L. Mambu, M. Labbaied, P. Grellier, R. David, R. Philippe, T. M. Mare and F. Frappier, *J. Nat. Prod.*, 2003, **66**, 1447.
140 D. Paola, B. Ivana, R. Carla, R. Marina, D. Paola, S. Luca and M. Luigi, *Flavour Fragrance J*, 2010, **26**, 34.
141 J. B. Harborne, C. A. Williams and K. L. Wilson, *Phytochemistry*, 1982, **21**, 2491–2507.
142 K. Arraki, P. Totoson, A. Decendit, A. Badoc, A. Zedet, J. Jolibois, M. Pudlo, C. Demougeot and C. Girard-Thernier, *J. Nat. Prod.*, 2017, **80**, 2432–2438.
143 P. Liu, L. Liu, Y. P. Tang, J. A. Duan and N. Y. Yang, *Chin. Chem. Lett.*, 2010, **21**, 606–609.
144 H. A. Quayyum, A. U. Mallik, D. M. Leach and C. Gottardo, *J. Chem. Ecol.*, 2000, **26**, 2221–2231.