# The Role of Aquatic Plants in Natural Products and Drug Discovery

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**ABSTRACT**

***Background***: Phytochemicals and their derivatives/analogues represent over 50% of the current medicines worldwide in clinical use. Despite a significant contribution to the total bioactive natural plant products, aquatic plants are underestimated, and several species are extinct and in the endangered list.

***Objective:*** The aim of this review article is to draw the attention of common people and scientists toward a few important contributions of the aquatic plants to natural product chemistry and drug discovery by highlighting the chemical and pharmaceutical aspects of the same.

***Methods:*** The presented data were collected and selected from the literature obtained by an online search for the ethnomedicinal properties, biological activities and bioactive chemical constituents of aquatic plants using Google Scholar, PubMed and Scifinder chemical abstract service.

***Results:*** The selected literature data revealed that the extract and compounds isolated from several aquatic plants possess significant biological/pharmaceutical properties. For example, the α-asarone (24) and asiatic acid (33) isolated from Acorus calamus and Centella asiatica, respectively, exhibited significant neuroprotective effects in vitro and in vivo. The cripowellin A (59), cripowellin C (60), cripowellin B (61) and cripowellin D (62), isolated from Crinum erubescens, exhibited potent antiplasmodial and antiproliferative activities with half maximal inhibitory concentration ($IC_{50}$) in nanomolar range (11-260 nM). Several other alkaloids from different Crinum species have also shown anticancer properties against different cancer cell lines with $IC_{50}$ value <5 µM. Alkaloids and resin glycosides, isolated from different Ipomoea species, have displayed significant psychotropic, psychotomimetic, anticancer, and antibacterial activities with IC50 value <5 µM.

***Conclusion***: The aquatic plants play a significant role in the discovery of bioactive natural products. Although several biological activities and bioactive compounds have been reported from these plants, further assessment and scientific validation of most of their traditional usages still need to be done. There are several other similar species that are

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underestimated and not much explored. Many aquatic plants, such as Ipomoea carnea Jacq., Juncus lomatophyllus Spreng., Commelina benghalensis Linn, Gunnera perpensa L., Scirpus maritimus L. and Mentha longifolia (L.) L., may be considered for further evaluation. In addition to these, one should not undermine the potential of Crinum macowanii for COVID-19 pathogenesis, as its chemical constituent lycorine has shown significant SARS-CoV-2 inhibitory potential (EC50, 0.3 μM; SI >129). Furthermore, most rural communities are still using the wetland resources for their cultural, medicinal, economic, domestic, and agricultural needs. Hence, the conservation of aquatic plants and wetlands is an issue of great concern.

**Keywords:** aquatic plants, ethnomedicinal usages, biological activities, bioactive compounds, conservation, and wetlands

## 1. INTRODUCTION

The most important and abundant natural sources, vital for human survival, are the diverse plant kingdoms. The plants have always been a rich source of food and medication for human being from human evolutionary era. Most of the people in the rural areas are still use traditional medicines to meet their primary health care needs. In addition, WHO has estimated that traditional medicine serves as primary health care needs of about 80% of the total world population and 85% of this traditional medicine comes from the medicinal plants. Even in modern health care system, natural products and their derivatives or analogues represent over 50% of all the drugs in clinical used in United States of America [1, 2].

Like terrestrial plants, aquatic plants not only prevent from the soil erosion, floods, and increased infiltration but also purify water by absorbing poisonous chemicals and heavy metals which are vital for their growth. These plants are also lethal for the pathogens that cause diseases in plants, animals, and humans [3]. Despite the significant contribution of medicinal plants to modern healthcare system, most of the herbal drugs and lead molecules come from the terrestrial medicinal plants [4-7]. However, aquatic plants often possess several biological activities and contain highly bioactive compounds; most of them are still unexplored in terms of their therapeutic potentials [8, 9]. Due to the lack of knowledge among rural communities about the medicinal benefits of the wetland resources, many wetlands have been degraded and destroyed over the years [10]. Several aquatic plants are drastically being harvested in non-protected wetlands. Due to this uncontrolled harvesting, several plants are getting extinct or endangered [11].

Due to this reason, international agencies, governments, local authorities' non-government organizations (NGOs), coastal communities and scientists are putting great emphasis on the ecological, environmental, and socio-economic importance of mangroves since past few years. Despite, the mangrove ecosystems provide a unique and valuable range of natural resources, huge areas of mangrove have been lost (especially in Southeast Asia and most parts of South Africa) due to wood extraction, conversion to agriculture, coastal aquaculture and salt production, coastal industrialization, and urbanization. More recently, shrimp farming has caused large scale losses of mangrove habitats in several countries, the worst cases being Ecuador, Indonesia, and the Philippines among others [12]. Hence, this review highlights the medicinal benefits of the aquatic plants for creating awareness among the society and emphasize thereby; for trying for conserving the mangroves and those plants with medicinal importance.

**Table-1. Biological activities of selected aquatic plants**

| Plant name | Plant part/Extract | Biological activities | References |
|---|---|---|---|
| *Acorus calamus* | Methanol extract of whole plant | Anti-germinating activity | [17] |
| | Essential oil of whole plant | Inhibition of adipogenesis in 3T3-L1 cells | [19] |
| | Essential oil of rhizomes | Insecticidal activity | [20] |
| | Hydroalcoholic extract and essential oil of rhizomes | Acetylcholinesterase inhibitory activity | [18] |
| | Alcoholic rhizome extract | Anthelmintic and antibacterial activity | [108] |
| | Methanol extract of leaves | Antineoplastic and Neurotrophic activities | [21] |
| | Ethanol extract of rhizome | Hepatoprotective activities | [15] |
| *Centella asiatica* | Ethanolic extract of whole plant | Wound healing, Venous insufficiency, Sedative, Anxiolytic, Antidepressant, Antiepileptic, Cognitive, Antioxidant, Anti-ulcer, Antinociceptive and Anti-inflammatory activities | [22] |
| *Commelina benghalensis* | Methanol extract of leaves | Antidiarrheal and Anthelmintic activity | [109] |
| | Different extracts of root and aerial parts | Analgesic and Anti-inflammatory activity | [110, 111] |
| | Different extracts of root | Hepatoprotective, antioxidant, anticancer and wound healing activities | [112-114] |
| | Methanol, ethanol and hexane extracts of leaves | DPPH Free Radical Scavenging activity | [115] |
| | Methanol extract of the whole plant | Antidiabetic activity | [116] |
| | Methanol extract of whole plant | Antinociceptive and Antidepressant activity | [117, 43] |
| | Methanolic extract of leaves | Thrombolytic and cytotoxic activity | [42] |
| | Aqueous-methanolic extract of aerial part | Sedative and anxiolytic effects | [41] |
| *Commelina diffusa* | Dichloromethane - methanol extract of whole plant | Cytotoxic, Antimicrobial and Antioxidant activities | [118] |
| | Methanolic extract of the whole plant | Central nervous system (CNS) depressant activity | [119] |
| *Crinum campanulatum*<br>*Crinum graminicola*<br>*Crinum macowanii*<br>*Crinum moorei*<br>*Crinum variabile* | Ethanolic extract of root and bulbs | Acetylcholinesterase inhibition | [120] |
| *Cyperus rotundus* | Ethanolic extract of rhizomes | Antiplatelet effects, Antioxidant activity | [53, 56] |
| | Methanol extracts from aerial parts | Antimutagens and Radical Scavengers | |
| | Methanol extract of rhizome | Antidiarrhoeal | [53] |

| | | | |
|---|---|---|---|
| | Essential oil of tuber | Antibacterial activity, Ovicidal & Larvicidal | |
| | Ethanol extract of tuber parts | Wound healing activity | |
| *Cyperus sexangularis* | Ethanolic extract of whole plant | Anti-elastase activity | [121] |
| *Cyperus marginatus* | | | |
| *Gunnera perpensa* L. | Methanolic extract of rhizomes | Antioxidant and cytotoxic activity | [59] |
| *Ipomoea cairica* | Methanol, ethanol and hexane extracts of leaves | DPPH Free Radical Scavenging Activity | [115] |
| | Ethanolic extract of aerial parts | Antinociceptive effect | [122] |
| *Ipomoea carnea* | Acetone extract of whole plant | Antibacterial activity | |
| | Aqueous leaf extracts | Antifungal activity | |
| | Extracts of flowers, leaves and stem | Antioxidant activity | |
| | Hexane, chloroform and ethyl acetate fraction of methanolic extract of whole plant | Anticancer activity | |
| | Polar and nonpolar extracts of whole plant | Anti-convulsant activity | |
| | Aqueous extract of whole plant | Immunomodulatory activity | |
| | Aqueous extract of leaves | Anti-hyperglycemic and hepatoprotective activity | [123] |
| | Methanolic and petroleum ether extracts of whole plant | Anti-inflammatory activity | |
| | Aqueous and methanolic extract of leaves | Anxiolytic activity | |
| | Petroleum ether, alcohol and aqueous extracts of leaf | Sedative activity | |
| *Ipomoea tyrianthina* | Dichloromethane extract of root | Antidepressant activity | [124] |
| *Juncus effusus* | Methanolic extract of whole plant | Antialgal activity | [69] |
| | Ethyl ether extract of whole plant | Cytotoxicity | [73,74] |
| *Juncus acutus* | Light petrol extract of whole plant | Antialgal activity | [72] |
| | Methanolic extract of rhizome | Antiinflammatory activity | [75] |
| | Ethanolic extract of aerial part | Anti-eczematic activity | [76] |
| *Mentha longifolia* | Aqueous-methanolic extract of whole plant | Antibacterial activity and Acute toxicity | [125] |
| | Aqueous extract of whole plant | Anti-nociceptive activity | |
| | Hexane extract of whole plant | Anti-inflammatory activity | |
| | Essential oil and crude methanolic extracts | Antimicrobial, anti-parasitical, insecticidal, antioxidant and anti-oxidative stress activity | [77] |
| | Hydroalcoholic extract of leaf | Gastrointestinal activity | |
| | Ethanolic extract of whole plant | Effects on genitourinary system | |

| | | | |
|---|---|---|---|
| *Nymphaea nouchali* | Methanolic extract of flower | Attenuation of melanogenesis, DNA protecting and antibacterial activities | [126, 95, 89] |
| | Methanolic extract of leaf | Antioxidant activity | [84] |
| | Aqueous alcoholic extract of flower | Antihepatotoxic effect | [85] |
| | Methanol extract of whole plant | Immunomodulatory effects | [127] |
| | Ethanolic and aqueous extracts of flowers | Anti-Hyperlipidemic Activity | [128] |
| | Ethanolic extract of seeds | Antidiabetic activity | [129] |
| | Aqueous extract of leaf | Antibacterial activity | [130] |
| | Hydroalcoholic seed extract | Antimicrobial activity | [87] |
| | Aqueous methanol extract of seeds and tuber | Postprandial antidysmetabolic and antioxidative stress properties | [131] |
| | Ethanolic extract of flower | Anti-acne activity | [88] |
| | | Antinociceptive and Anti-depressant like activities | [132] |
| *Nymphaea tetragona* | Methanolic extract of the whole plant | Modulation of quorum sensing-controlled virulence factors | [133] |
| *Persicaria salicifolia* *Persicaria senegalensis* | Methanolic extract of seed | Antitumor activity | [134] |
| *Scirpus maritimus* | Ethanol extract of seeds | Hepatoprotective, antifungal, ichthyotoxic and antileukemic activity | [97] |
| *Typha capensis* | Acetone extract of leaf | Anti-inflammatory and antioxidant properties | [135] |
| | Rhizomes and leaves | Free radical scavenging activity, collagenase inhibitory activity and effects on human sperm motility and mitochondrial membrane potential | [136] |
| *Zantedeschia aethiopica* | Ethyl acetate extract of whole plant | Antialgal activity | [99] |

## 2. TRADITIONAL USES, BIOLOGICAL ACTIVITIES AND BIOACTIVE COMPOUNDS OF SELECTED AQUATIC PLANTS

One of the best-known examples of traditional uses of the wetland plants is the use of Willows. Native Americans use these plants for the same purposes for which modem practitioners use its active compound, salicylic acid and its derivative aspirin i.e., for fever, headache, muscle pain, menstrual cramps, rheumatoid arthritis, osteoarthritis, gout, and ankylosing spondylitis etc. [13]. Hence, a detailed literature search was done for traditional usages, biological activities and bioactive constituents of aquatic plants using scientific search engines such as Google scholar, PubMed and Scifinder. The role of twelve most explored plants in traditional medicines, natural products and natural products-based drug discovery is discussed in this manuscript. Those, which were partially explored, with limited scientific evidence, were ignored. A list of biological activities different extracts of different plant parts is given in table-1.

### *2.1. Acorus calamus L.*

Another common wetland plant, *Acorus calamus* (sweet flag), is being widely used for fevers, stomach cramps and colic; the rhizome is chewed for toothache and powdered rhizome is inhaled for congestion in North America. In Indian Ayurvedic medicine, it is used as a rejuvenator for the brain and nervous system, and as a remedy for digestive disorders [1]. *Acorus calamus* is cultivated in South Africa since early colonial times across stream banks and in wetlands. The plant is well known for its diverse biological activities and several bioactive compounds have been identified from the plant.

The biological activities such as, sedative and hypnotic effect, CNS depressant activities, anticonvulsant activity, acetylcholinesterase-inhibitory and memory-enhancing effect, anti-inflammatory activity, antioxidant activity, cardiovascular activity, hypolipidemic activity, actions on respiratory system, anticancer activity, immunosuppressive activity, antiulcer and cytoprotective properties, antidiarrheal activity, antispasmodic activity, antibacterial activity, antifungal activity, antiviral activity, anthelmintic activity, insecticidal activity, piscicidal activity, adulticidal activity, diuretic activity and insulin sensitization activity have been reported earlier which reflect the medicinal values of this aquatic plant [14].

Eight sesquiterpenes, calamusin A-H (**1-8**) and a norsesquiterpene, calamusin I (**9**) have been isolated from the ethanol extract of *Acorus calamus* rhizomes (Fig.1). The calamusin C (racemic mixture of **3a** and **3b**), calamusin D (**4**), calamusin G (**7**) and **9** exhibited weak hepatoprotective activities against paracetamol or acetaminophen (APAP)-induced HepG2 cell damage at 10 μM concentration. However, calamusins A (**1**), B (**2**), E (**5**), F (**6**) and H (**8**) were found to be not active [15].

Three other sesquiterpenes, 1β,7α(H)-cadinane-4α,6α,10α-triol (**10**), 6β,7β(H)-cadinane-1α,4α,10α-triol (**11**) and 1α,5β-guaiane-10α-*O*-ethyl-4β,6β-diol (**12**) were also isolated from rhizome of *Acorus calamus* [16]. However, no biological activities of these compounds were evaluated. Due to their close similarity with other sesquiterpenes isolated from the plants, these compounds can be evaluated for their hepatoprotective potential. The sesquiterpenes **13-23** along with α-asarone (**24**), asaraldehyde (**25**), 1-(2,4,5- trimethoxyphenyl)-propane-l,2-dione (**26**) and 1-(2,4,5-trimethoxyphenyl)-1-methoxypropan-2-ol (**27**) were isolated form the methanol extract of Acorus calamus. Of these, 1-hydroxyepiacorone (**16**) and **24** exhibited potent anti-germination activities against the several seeds while, acoronene (**17**) and epiacoronene (**18**) exhibited a weak activity against the same [17].

The α-asarone (**24**) exhibited potent acetylcholinesterase inhibitory activity with the half maximal inhibitory concentration ($IC_{50}$) value of 3.33 μM [18]. The β-asarone (**28**), a component of *Acorus calamus* essential oil, exhibited potent anti-obesity activity by exerting significant inhibitory effect against adipogenesis in 3T3-L1 cells [19]. The methyleugenol (**29**), (E)-methylisoeugenol (**30**) and **24** possess potent insecticidal activity against Liposcelis bostrychophila booklouse [20]. Two lignans, epieudesmin (**31**) and galgravin (**32**) have also been identified in methanolic extract of the plant. The epieudesmin has shown antineoplastic activity against the murine P388 lymphocytic leukemia cell line, human pancreatic cancer cell line (BxPC-3), human breast cancer cell line (MCF-7), human glioblastoma cell line (SF268), human lung cancer cell line (NCI-H460), colon cancer cell line (KM20L2) and human prostate cancer cell line (DU145). The galgravin has demonstrated activity in preventing neuronal death and stimulating neurite growth. Structurally similar lignans have also shown neuroprotective activity in *in-vitro* models for Alzheimer's and Parkinson's disease [21].

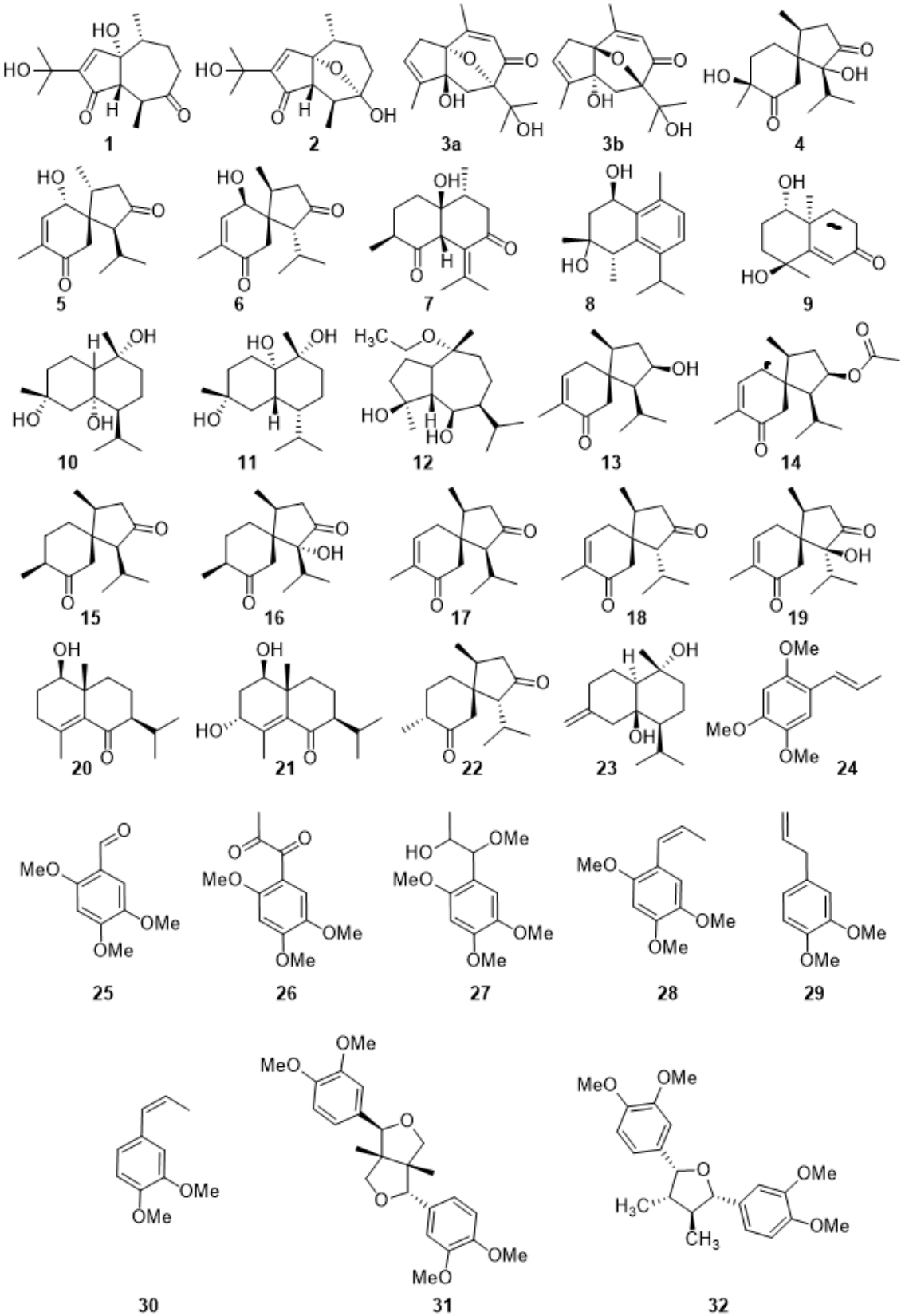


**Fig. 1.** Bioactive constituents from *Acorus calamus.*

### *2.2. Centella asiatica (L.)*

*Centella asiatica* (L.) (Apiaceae) is used for the treatment of leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhea, fever, amenorrhea, diseases of the female genitourinary tract and for relieving anxiety and improving cognition [22]. It is also used for wound healing, cleaning up skin infections, burn and scar treatment, the treatment of arthritis and rheumatism. In ayurvedic medicine, it has been used as a mild diuretic, memory enhancer as well as for the treatment of anxiety, stress and liver and kidney problems. It is also used as a general health tonic, an aphrodisiac and immune booster and a medication for bronchitis and asthma [23].

The ethanolic extract of *C. asiatica* (CA) leaves, displayed the larvicidal and adult emergence inhibitory activity against mosquito *Culex quinquefasciatus*. Toxicity of this extract was found to increase with temperature (19-31°C) and the median lethal concentrations ($LC_{50}$) ranged between 6.84-1.12 ppm. At the $LC_{50}$ concentrations, at different temperature, this extract inhibited the adult emergence by 90.8-97.8% [24]. The aqueous and alcoholic extracts of CA exhibited prominent antiallergic, anti-pruritic and anti-inflammatory activities *in vivo* in Albino rats at a dose of 100 mg/kg body weight [25]. The ethanolic extract of CA displayed a significant anti-ulcerogenic activity (comparable to omeprazole) against ethanol-induced gastric mucosal injury in Sprague Dawley adult male rats at 100, 200 and 400 mg/kg body weight [26].

In addition, CA has shown *in-vitro* neuroprotective, wound healing, anti-inflammatory, antipsoriatic, hepatoprotective, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial, insecticidal, antifungal, antioxidant activities and used for the lepra and venous deficiency treatments [27]. CA is reputed for its beneficial effects in various neurological disorders [28]. The effect of hydro-ethanolic (70%) extract of CA on generalized anxiety disorder in man was evaluated by Jana et al. 2010 [29]. Participants were medicated with the CA in a fixed dose regime (500 mg/capsule, twice daily, after meal). The observations revealed that, CA not only significantly ($p<0.01$) attenuated anxiety related disorders but it also significantly ($p<0.01$) reduced the stress phenomenon and its correlated depression. It further improved the willingness for adjustment and cognition significantly ($p<0.01$).

Asiatic acid (AA, **33**) is the most important constituent of CA responsible for its neuroprotective effects. It has shown neuroprotective effect in a mouse model of focal cerebral ischemia [30]. AA has also been reported to attenuate glutamate-induced cognitive deficits of mice at a dose of 100 mg/kg body weight and significantly protected human neuroblastoma (SH-SY5Y) cells against glutamate-induced apoptosis *in-vitro,* at a concentration of 10 nM [31]. In another study, AA has shown neuroprotective effect on rotenone-induced mitochondrial dysfunction and oxidative stress mediated apoptosis in differentiated SHSYS5Y cells [32]. 5-Fluorouracil (5-FU) is a chemotherapeutic medication for the treatment of cancer. However, the induction of memory deficits in treated patients is a major side effect of 5-FU. Interestingly, when male Sprague Dawley rats were treated with AA and 5-FU at a dose of 30 and 25 mg/kg body weight, respectively, a lower decrease in sex determining region Y-box 2 (SOX2), nestin, doublecortin (DCX), and nuclear factor erythroid 2-related factor 2 (Nrf2) levels were observed. This result showed that AA could counteract the downregulation of neurogenesis within the hippocampus and memory deficits caused by 5-FU via inhibiting oxidative stress and increasing neuroprotective properties [33]. AA has been exerted a notable neuroprotective effect in rat model of focal embolic stroke at a dose of 75 mg/kg body weight. These neuroprotective effects were partially associated with reduction of apoptosis-inducing factor and cytochrome c releases [34]. Furthermore, AA effectively inhibited the growth of human Hep G2 liver cancer cells in concentration dependent manner. The best result found was, inhibition of cells by 85% at the concentration of 50 µg/ml [35].

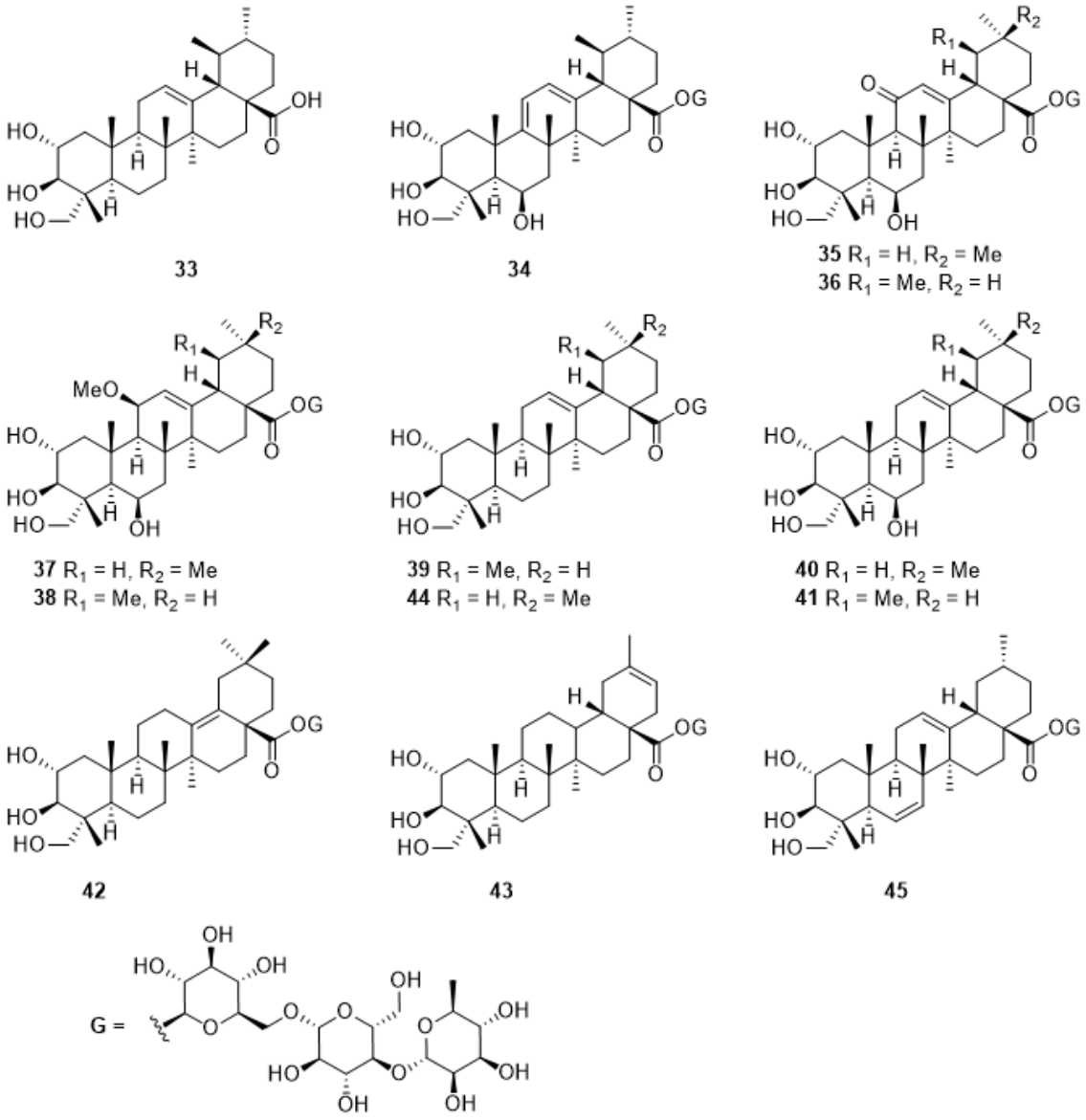


**Fig. (2a)**. Bioactive constituents of *C. asiatica.*

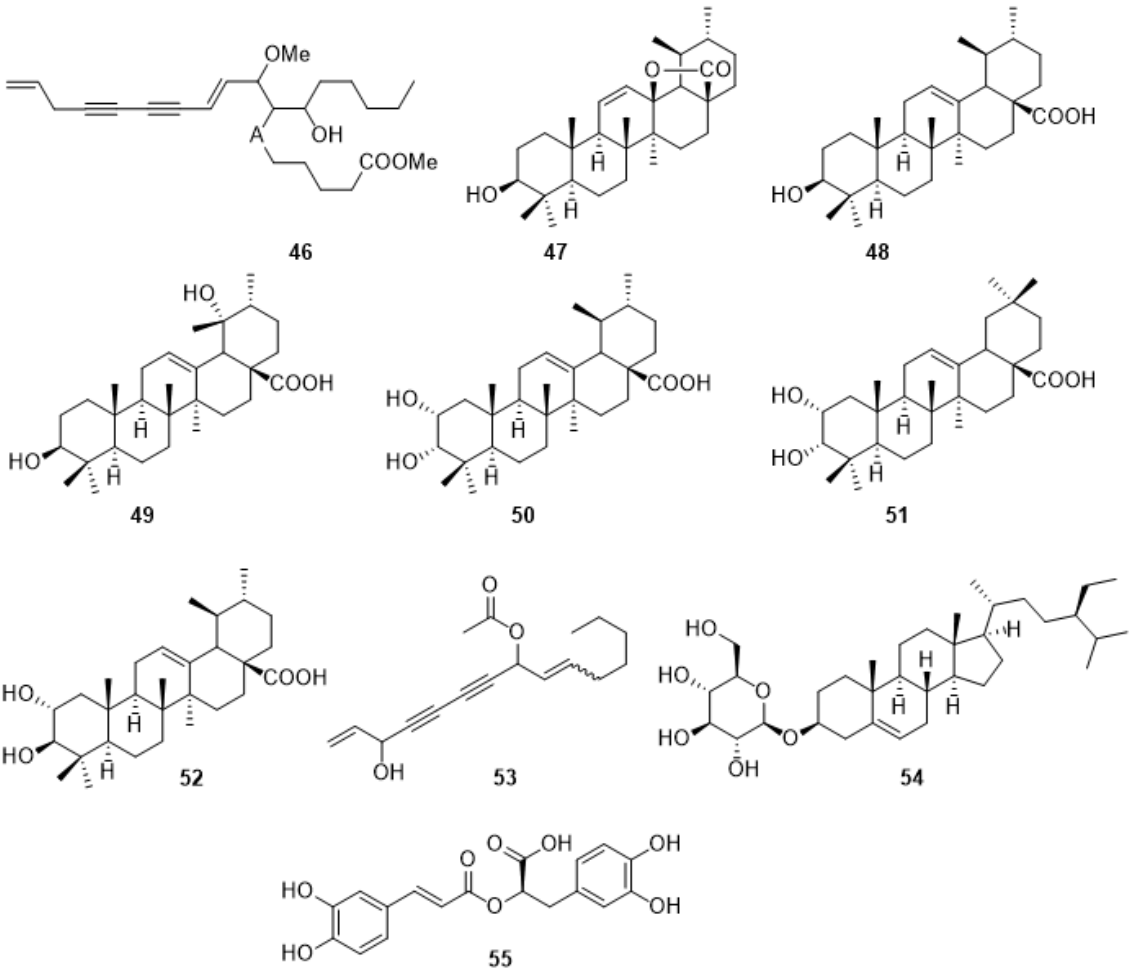


**Fig. (2b)**. Bioactive constituents of *C. asiatica.*

Eleven other oleanane- or ursane-type pentacyclic triterpenoid saponins (Fig. 2a), centelloside G (**34**), 11-oxo-asiaticoside B (**35**), 11-oxomadecassoside (**36**), 11(β)- methoxy asiaticoside B (**37**), 11(β)-methoxy madecassoside (**38**), asiaticoside (**39**), asiaticoside B (**40**), madecassoside (**41**), centellasaponin A (**42**), isoasiaticoside (**43**), scheffoleoside A (**44**), and centelloside E (**45**) also displayed the neuroprotective effect by increasing cell viability of 6-hydroxydopamine hydrobromide (6-OHDA) treated PC12 cells at the concentration of 100 µM. Moreover, compound **35** also attenuated cell apoptosis and increased the mRNA expression of antioxidant enzymes, including superoxide dismutase and catalase. Additionally, compound **35** activated the phosphatidylinositol 3-kinase/Akt pathway, including PDK1, Akt, and GSK-3β. All these compounds were isolated from the 80% MeOH extract of the whole plant of *C. asiatica* [36]. Madecassoside (**41**) has also been reported to exert neuroprotective effect ($IC_{50}$, 2.5 µg/mL) in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cellular toxicity assay with increased cell viability [37].

One polyacetylene compound, methyl 5-[(*E*)-9-hydroxy-1-(1-hydroxyhexyl)-2-methoxy-undeca-3,10-diene-5,7-dienyloxy]pentanoate (**46)** was isolated from the aerial part of the *C. asiatica* (Fig. 2b) . This compound induced apoptosis by 63%, independent of cell cycle regimen in mouse lymphoma cells (P388D1) with $IC_{50}$ value of 24 µM. The compound also reduced the nitric oxide (NO) production (72%) in lipopolysaccharide-activated mouse macrophages at concentration of 24 µM with no measurable cytotoxicity [38]. 11,12-Dehydroursolic acid lactone (**47**), ursolic acid (**48**), pomolic acid (**49**), 2α,3α-dihydroxyurs-12-en-28-oic acid (**50**), 3-epimaslinic acid (**51**), asiatic acid (**33**), corosolic acid (**52**), 8-acetoxy-1,9-

pentadecadiene-4,6-diyn-3-ol (**53**), β-sitosterol 3-*O*-β-D-glucopyranoside (54) and rosmarinic acid (**55**), isolated from CA exhibited weak antiproliferative activity against human gastric adenocarcinoma (MK-1), human uterine carcinoma (HeLa) and murine melanoma (B16F10) cancer cell lines with the concentration for 50% of maximal inhibition of cell proliferation (GI50) between 8-173 µM [39].

The other compounds isolated from this plant includes few other acetylenes, fatty acids, alkaloids, flavonoids, flavonoid glycosides, steroids, and steroid glycosides, phenolics, pentacyclic triterpenes and their glycosides [40, 23, 27, 28].

### *2.3. Commelina benghalensis* Linn

*Commelina benghalensis* Linn (family Commelinaceae) is used against mouth thrush, inflammation of the conjunctiva, epilepsy, psychosis, insanity, nose blockage in children, suppurativa sores, snake bite, swelling, burns and exophthalmia. It is also used as a diuretic, febrifuge, and laxative [41].

The methanolic extract of *C. benghalensis* leaves has been reported to exhibit the notable cytotoxic properties in brine shrimp lethality assay with $LC_{50}$ value of 278.69 µg/mL compared with standard vincristine sulphate ($LC_{50}$, 0.512 µg/mL) and significant thrombolytic activity with average percentage clot lysis of 40.94% compared with standard streptokinase (75%) [42]. The chloroform, petrolium ether, *n*-butanol and hydromethanol soluble fractions of the aerial parts of *C. benghalensis* exhibited dose dependent sedative and anxiolytic properties *in-vivo*. The chloroform fraction was the best active fraction and showed almost equal effect at a dose of 200 and 400 mg/kg, p.o. to that exhibited by the positive control (diazepam) at 1 mg/kg, p.o. [41]. The methanol extract of *C. benghalensis* showed significant anti-depressant activity by decreasing the immobility times of Swiss albino mice compared to control, at a dose of 200 and 400 mg/kg body weight p.o. in forced swimming and tail suspension tests [43].

Dammara-12-en-3-one (**56**), stigmasterol (**57**) and 3-*O*-(2,3,4,5,6-pentahydroxy)-cinnamoyl dammara-12-ene (**58**) were isolated from the *n*-hexane fractionate of methanol extract of *C. benghalensis* (Fig. 3). In a DPPH radical scavenging assay, the $IC_{50}$ values were predicted to be 790.18, 4186.94 and 2001.16 µg/mL for 56, 57 and 58 respectively, whereas positive control (ascorbic acid) showed $IC_{50}$ value of 1.26 µg/mL [44]. A few other chemical constituents identified in *C. benghalensis* have also been reported [45].

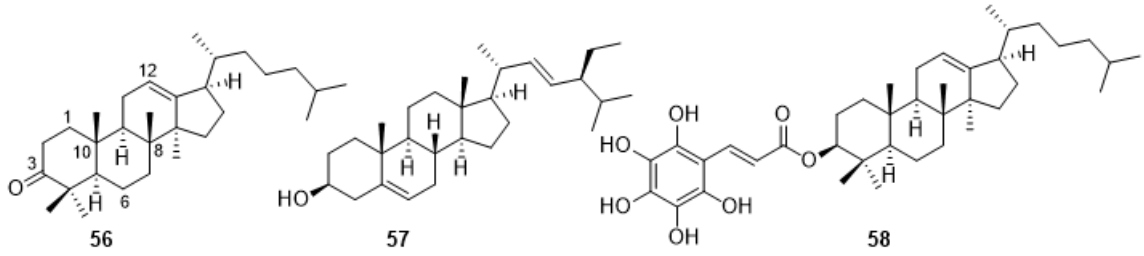


**Fig. (3)**. Bioactive constituents of *C. benghalensis.*

### *2.4. Crinum*

The genus *Crinum* belongs to the Amaryllidaceae family. There are approximately 160 known species under this genus. The extracts of *Crinum* species have been used traditionally to treat a variety of ailments including fever, pain management, swelling, sores and wounds, cancer, and malaria [46]. Most of the species were used traditionally as laxatives, emetic, diaphoretic, emollient, expectorants, diuretics, urinary troubles purgatives and tonics. The plant species were also used to treat rheumatism, fever, coughs and colds, abscesses, chest ailments, snake bite, earache, skin diseases and inflammation. The other traditional usages also include the treatment of renal and hepatic conditions, aching joints, septic sores, varicose veins, kidney and bladder infections, sexually transmitted diseases, and backache.

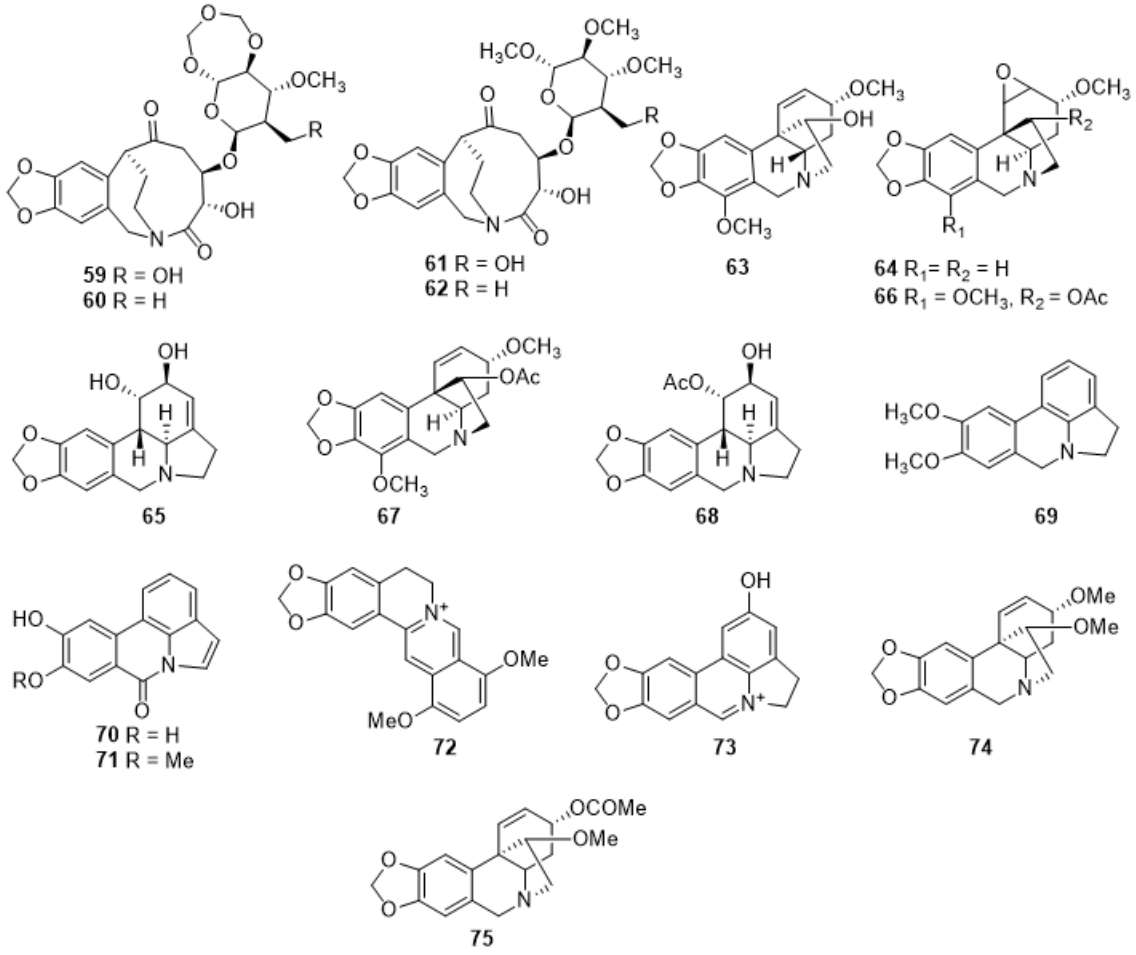


**Fig. (4).** Selected bioactive alkaloids form *Crinum* species.

The *Crinum* species are also very well-known and pharmaceutically explored plant species. The plant species and its chemical compounds have shown interesting biological properties such as, antitumor, immunostimulant, antibacterial, antifungal, cytotoxic, antiparasitic, insecticidal and anti-Alzheimer's disease activity. The alkaloids are the major bioactive components of these plant species. The cripowellin A (**59**), cripowellin C (**60**), cripowellin B (**61**) and cripowellin D (**62**), isolated from *Crinum erubescens* have been reported as potent antiplasmodial and antiproliferative agents.

The antiplasmodial $IC_{50}$ values for compounds **59-62** were in the range of 26-260 nM whereas; those against the A2780 human ovarian cancer cell line were between 11-28 nM [46, 47]. Similarly, (+)-crinamine (**63**), (-)-augustine (**64**) and (-)-lycorine (**65**), isolated form *Crinum amabile* have shown potent antiplasmodial against *Plasmodium falciparum*. The

antiplasmodial $ED_{50}$ values of compounds were in the range of 0.14-2.18 µg/mL. These three compounds (63-65) also exhibited cytotoxicity against human breast cancer (BCA-1), human fibrosarcoma (HT-1080), human lung cancer (LUC-1), human melanoma (MEL-2), human colon cancer (COL-1), human oral epidermoid carcinoma (KB), vinblastine-resistant KB (KB-V1), murine lymphoid (P-388), human epidermoid carcinoma (A-431), hormone-dependent human prostate cancer (LNCaP), hormone-dependent human breast cancer (ZR-75-1) and human glioblastoma (U-373); $IC_{50}$, 0.3-6.9 µg/ml [48]. 11-*O*-Acetyl-1,2-β-epoxyambelline (**66**) and 11-*O*-acetylambelline (**67**), isolated from *C. latifolium* showed immunomodulatory activity in combination (1:1) with each other [49]. The 1-*O*-Acetyllycorine (**68**), isolated from *C. moorei* and assoanine (**69**) has been reported to be a potent inhibitor of acetylcholinesterase enzyme [50].

The criasiaticidine A (**70**), pratorimine (**71**) and lycorine isolated from *C. asiaticum* var. japonicum possessed activity against Meth-A (mouse sarcoma) and Lewis lung carcinoma (mouse carcinoma) tumor cell lines (LLC) with median effective dose ($ED_{50}$), 0.3-4.2 µg/ml [51]. The crinumaquine (**72**), lycorine, ungeremine (**73**), 11-*O*-methylcrinamine (**74**), 3-*O*-acetylhamayne (**75**) and crinamine (Fig. 4) isolated form the chloroform and ethylacetate-soluble fractions of an ethanol extract of the bulbs of *Crinum asiaticum* L. var. sinicum Baker showed remarkable cytotoxicity against human lung cancer (A549), human colon cancer (LOVO), human leukaemia (HL-60), and acute lymphocytic leukaemia (6T-CEM) cell lines with $IC_{50}$ values between 0.17-9.15 µg/ml [52].

### *2.5. Cyperus rotundus* L.

*Cyperus rotundus* has been used widely in traditional herbal medicine as analgesic, sedative, antispasmodic, antimalarial, stomach disorders and to relieve diarrhea. The tuber part of the plant is one of the oldest known medications used for the treatment of dysmenorrheal and menstrual irregularities. Infusion of this herb has been used in pain, fever, diarrhea, dysentery, as an emmenagogue and in other intestinal problems. The rhizomes of *Cyperus rotundus* are used as traditional folk medicines for the treatment of stomach, bowel disorders and inflammatory diseases.

It has also been reported to possess various biological activities such as antimalarial, antidiarrheal, antidiabetic, antibacterial, antioxidant, wound healing, ovicidal and larvicidal activities. These biological activities and several bioactive chemical compounds identified and isolated from this plant, validate most of its traditional uses [53]. The *n*-hexane, chloroform, ethyl acetate, methanol, and water extract of *C. rotundus* rhizome displayed significant free radical scavenging activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay with $IC_{50}$ values ranging between 28.35-111.18 µg/ml. The $IC_{50}$ value for positive control (ascorbic acid) was found to be 10.98 µg/ml. However, the most active methanol extract ($IC_{50}$, 28.35) also displayed a potent cytotoxic effect against human breast cancer (MCF-7), cervical cancer (HeLa), liver cancer (Hep G2), prostate cancer (PC-3) and colorectal adenocarcinoma cancer (HT-29) cell lines at much lower $IC_{50}$ values of 4.52, 6.83, 7.66, 8.34 and 9.85 µg/mL, respectively. However, this extract was non-toxic to the normal cell line (MCF-12A) up to 200 µg/ml concentration [54].

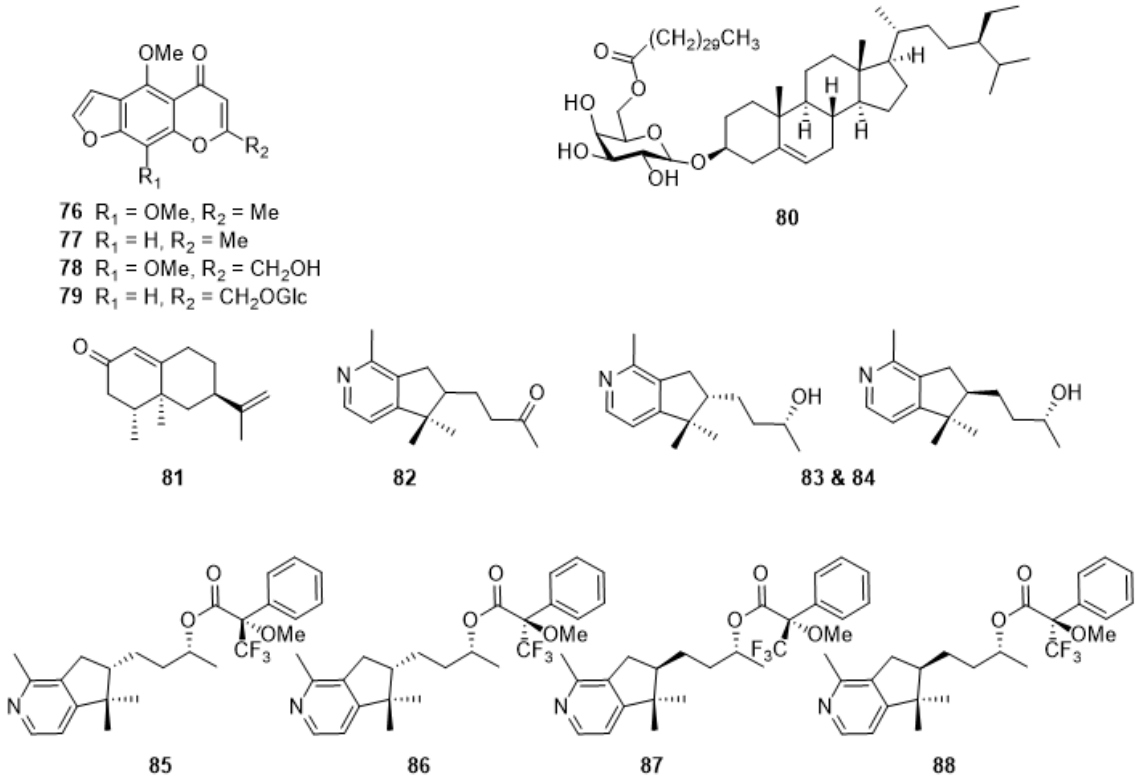


**Fig. (5).** Bioactive compounds of *C. rotundus*.

The hexane extracts of most of the *Cyperaceae* species have been reported to exhibit antifeedant activities against the tobacco cutworm (*Spodoptera litura*). Few furochromones and steryl glycosides; isolated from the methanol extract of *C. rotundus* aerial parts (Fig. 5) have shown antifeedant and cytotoxic activities. The furochromones, khellin (**76**), visnagin (**77**), ammiol (**78**) and khellol-β-D-glucopyranoside (**79**) exhibited 99.5, 96.9, 33.1 and 39.5% inhibition of larval growth of the vigorous pest insect Spodoptera littoralis respectively, at the concentration of 1.2 mg. These results suggested that the oxidation of methyl group at position C-2 results in the reduction of the antifeedant activity. Furthermore, visnagin (**77**), sitosteryl (6'-hentriacontanoyl)-β-D-galactopyranoside (**80**) and **76** showed significant cytotoxic activity against L5178y mouse lymphoma cells with median effective dose ($ED_{50}$) value of 0.9, 4.2 and 4.5 µg/ml respectively. These compounds were also active in the brine shrimp lethality test and at the 20-50 µg/ml concentrations [55]. The (+)-nootkatone (**81**), isolated form the ethanolic extract has shown significant antiplatelet effects. It is the most important and expensive constituent of grapefruit. It also possesses significant insecticidal property and is commonly used in foods, cosmetics, and pharmaceuticals [56]. Seven alkaloids including rotundines A-C (82-84) and (S)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) and (R)-MTPA esters of rotundines B and C (**85-88**) have also been isolated from the methanolic extract of rhizomes of *C. rotundus* [57].

### *2.6. Gunnera perpensa* L.

*Gunnera perpensa* is traditionally used for the treatment of venereal diseases, infertility, endometritis, urinary tract problems, impotence, cold, menstrual pain, wounds, and psoriasis. Most South African women use decoctions of the root for female fertility and good infant development as well [58]. The methanolic extract of *Gunnera perpensa* has been reported to possess a weak cytotoxicity to brine shrimp larvae. The median lethal concentration ($LC_{50}$) was found to be 137.62 mg/ml [59]. Later, a phenylpropanoid glycoside, Z-venusol (**89**) isolated from *Gunnera perpensa* demonstrated a statistically significant, concentration-

dependent, apoptotic inhibitory effect on proliferation of MCF-7 cells, with an $IC_{50}$ of 53.7 µg/ml after 72 h exposure. The percentage inhibition was found to be 69% at highest concentration (250 µg/ml) used [60].

Few other phenyl propanoids, (*E*)-lespedezic acid (**90**), (*Z*)-lespedezic acid (**91**) and (*Z*)-methyl lespedezate (**92**) glycosides along with ellagic acid (**93**), trimethyl ellagic acid (**94**) and trimethyl ellagic acid-β-D-glycoside (**95**) have been isolated from *G. perpensa* (Fig. 6) [61, 62]. The ellagic acid and its similar glycosidic derivative, 4'-*O*-methylellagic acid 3-(2",3"-di-*O*-acetyl)-α-L-rhamnoside (**96**) have also shown remarkable anticancer properties against various cancer cell lines [63-66]. This result justifies the cytotoxicity reported for the plant extract by Simelane et al. 2010.

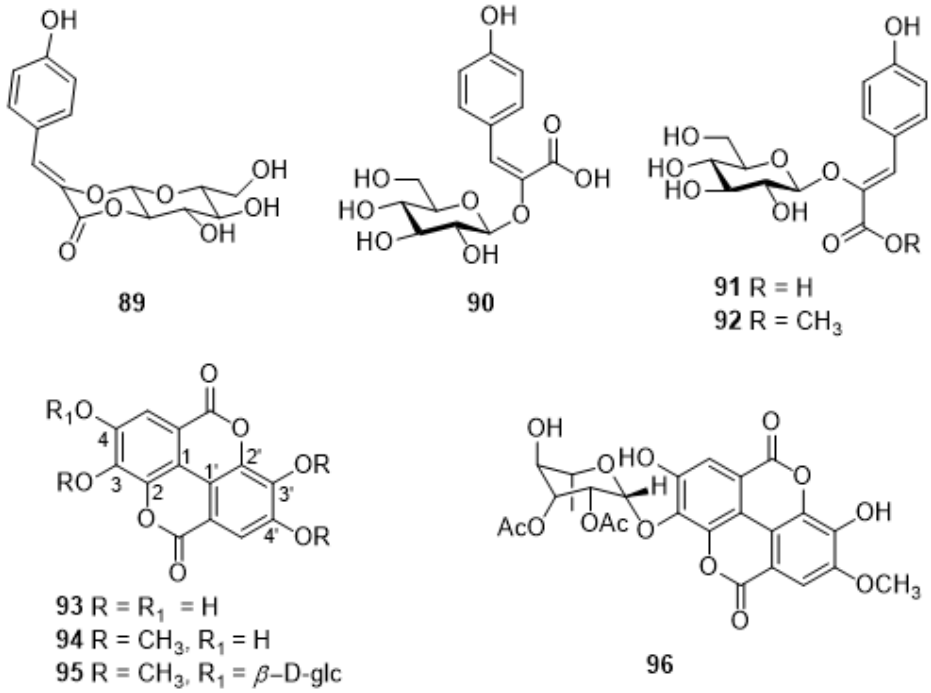


**Fig. (6).** Bioactive compounds of *G. perpensa*

### *2.7. Ipomoea*

*Ipomoea* is a genus of approximately 600-700 aquatic plant species in Convolvulaceae family. These species have been used by traditional healers of all over the worlds for the treatment of several diseases like, diabetes, hypertension, dysentery, constipation, fatigue, arthritis, rheumatism, hydrocephaly, meningitis, kidney ailments and inflammations. Different plant species of *Ipomoea* have shown diverse pharmaceutical properties and a few bioactive chemical components have been isolated from these plant species. Several species of the genus have the phytotoxic property and root of most of the species is used to treat constipation. Several species contain ergot type alkaloids, which are psychoactive and thus these species are used as hallucinogenics.

A few selected bioactive compounds are presented in Fig. 7. Compounds **97-99**, isolated from several *Ipomoea* species, have shown psychotropic and psychotomimetic activities. The 2-epi-lentiginosine (**100**) and swainsonine (**101**), isolated from *I. carnea*, potentially inhibit lysosomal α-mannosidase in rat ($IC_{50}$, 4.6 and 0.02 µM respectively). Compound **101** also exhibited immunomodulatory and antimetastatic activities. The glycoresins, ipomoeassins A-

E (**102-106**), which were isolated from the leaves of *I. squamosa*, showed cytotoxicity against human ovarian (A2780) cancer cell line ($IC_{50}$, 0.035 to 3.3 µM). The compound **107**, isolated from the roots of *I. murucoides* presents marginal activity against ovarian carcinoma (OVCAR-5) cells with median effective dose ($ED_{50}$) of 5.0 µg/mL. The stansin 5 (**108**) also possessed citotoxicity against ovarian and cervical carcinomas by $ED_{50}$, 1.5 and 4.0 µg/mL respectively. The tricolorin A (**109**) has been reported for phytotoxicity and antibacterial activity against *Staphylococcus aureus* and strong cytotoxic activity against human breast cancer ($ED_{50}$, 2.2 µg/mL). Apart from this, several other compounds have also been isolated from *Ipomoea* species and have shown diverse biological activities [67].

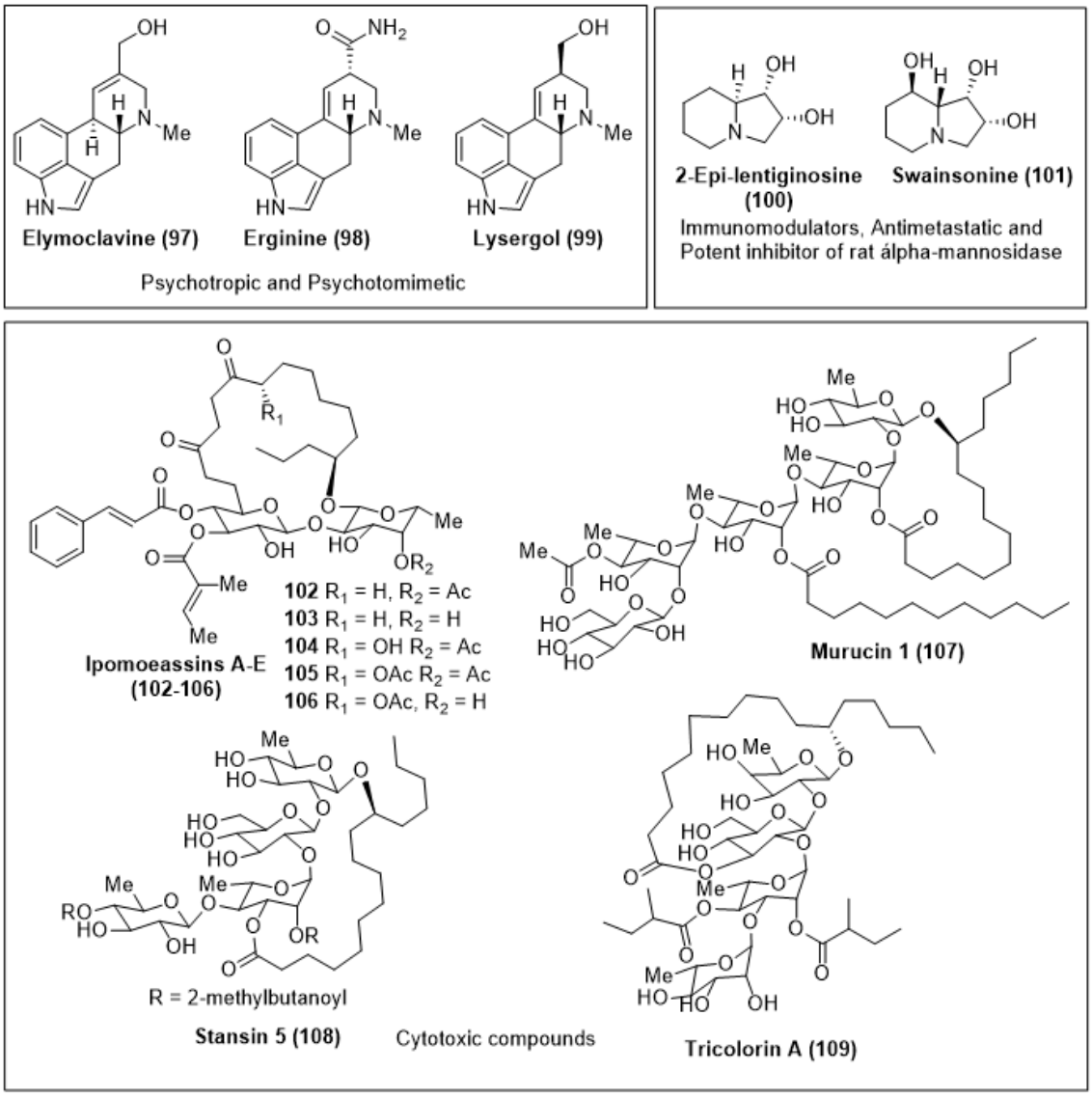


**Fig. (7).** Selected bioactive compounds from *Ipomoea* species.

### *2.8. Juncus* L.

The *Juncus* L. is an important aquatic medicinal plant belonging to Juncaceae family. The different parts of several *Juncus* species have been traditionally used as a remedy for diarrhea,

cold, fever and insomnia and as a sedative agent. The Juncus species are well known aquatic plants indigenous to South Africa. However, the indigenous African species are less explored with regards to the biological activities and the chemical components than the others. Therefore, the protection of these plant species is highly needed for the research purposes as well. *J. effusus* is used traditionally in Japan, China, and Taiwan as an antipyretic and antiphlogistic agent. Several, African and non-African *Juncus* species and their chemical constituents have shown diverse biological activities such as, cytotoxic, antitumor, antioxidant, hepatoprotective, antiviral, antimicrobial, anti-algal, anti-inflammatory, and anti-eczematic activities. The phenanthrenes, dihydrophenanthrenes, dihydrodibenzoxepin, pyrenes, steroids, flavonoids, stilbenes and terpenes are the major constituents of the *Juncus* species [68]. Selected bioactive compounds from the species are demonstrated in Fig. 8. The 9,10-dihydrophenanthrenes **110-116**, **121-123** and **127**, isolated from *Juncus effusus* and *Juncus acutus*, possessed anti-algal activity against green alga *Selenastrum capricornutum* with $IC_{50}$ values of <20 µM [69-72].

The compounds 113, 114, 122, 124, 117-120, 125, 126 and 128 [Fig. 8], isolated from *Juncus effuses* possessed potent cytotoxicity in brine shrimp lethality assay with the median lethal dose ($LC_{50}$) values of <10 µg/ml [73, 74]. The 9,10-dihydrophenanthrenes **114**, **116** and jancutol (**129**) also exerted anti-inflammatory effect by inhibiting the expression of inducible nitric oxide synthase (iNOS) in lipopolysaccharide-stimulated RAW264.7 macrophage cells [75]. Two phenolic glycosides, markhamioside F (**130**) and canthoside B (**131**), isolated from the alcoholic extract of *Juncus acutus*, possessed significant anti- eczematic activity. The alcoholic extract itself, cure eczema by 80 and 100% at 4% and 6% concentrations in Vaseline, respectively, while compounds **130** and **131** cure by 90% and 100% respectively at a concentration of 2% [76].

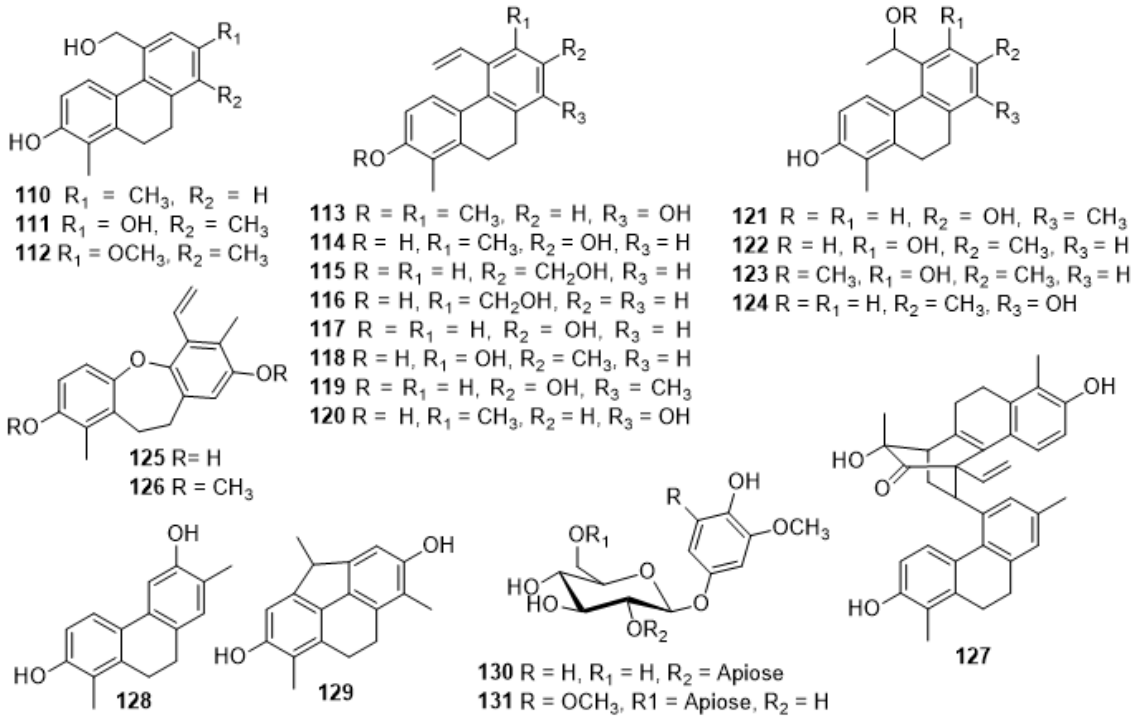


**Fig. (8).** Selected bioactive compounds from *Juncus* species.

## *2.9. Mentha longifolia* (L.) L.

The *Mentha longifolia* has been used as a traditional and folk medicine for the treatment of a wide range illness. It was used for the treatment of constipation, fever, nausea, bronchitis, common cold, cough, peptic and intestinal ulcer, general weakness, wound healing, inflammation, and liver disorders. *M. longifolia* was also used for the treatment of sore throat, eye diseases, minor mouth and throat irritation, aches, sprains, gut spasm, nasal decongestants, diarrhea, and other gastrointestinal disorders. Further, it was used as an anti-parasitic, anthelmintic, antimicrobial, analgesic, emmenagogue, carminative, anti-emetic, sedative, and digestive medicament [77].

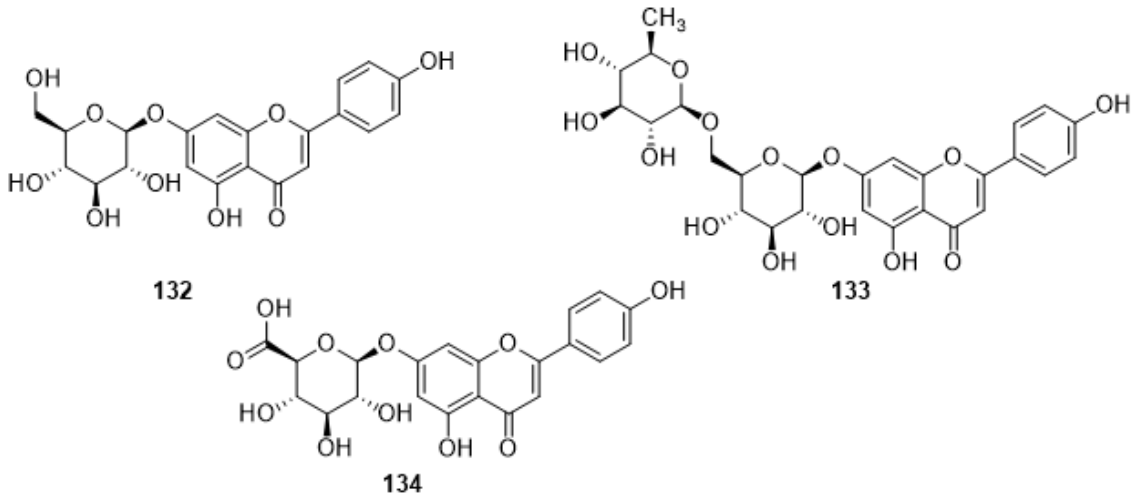


**Fig. (9).** Cytotoxic compounds from *M. longifolia.*

The cytotoxicity of *Mentha longifolia* extracts, essential oils and the flavonoid glycosides against various cancer cell lines have been reported by several groups. Three flavonoids, apigenin-7-*O*-glucoside (**132**), apigenin-7-*O*-rutinoside (**133**) and apigenin-7-*O*-glucuronide (**134**) have been identified as the main cytotoxic constituent of this species (Fig. 9) [78, 79].

## *2.10. Nymphaea*

*Nymphaea nouchali* Burm.f., also known as *Nymphaea stellata* Willd. (Nymphaeaceae) is used to cure various diseases like, urinary tract infection, diarrhea, dyspepsia, heart diseases, fever, and enteritis in Indian Ayurvedic system [80]. In folk medicine, it is used as a tranquilizer, plausible detoxicant, and has shown soothing and various astringent effects. The flower, leaf, and root have traditionally been used for the treatment of diabetes, eruptive fever, dysentery, and disorders of the heart and blood, as well as used as cardiotonic, diuretic, narcotic, and aphrodisiac [81-83]. The leaf and rhizome have been used for the treatment of kidney related disorders [84, 85]. The plant is also used in the Ayurveda and Siddha system of medicine for the treatment of inflammation, menorrhagia, blennorrhagia, liver disorders, menstruation problem, and cutaneous diseases and as a bitter tonic [86, 87]. The seeds are used as stomachic, restorative and antidiabetic medicament [88]. *N. nouchali* is also used for the treatment of indigestion and tumor [89-91].

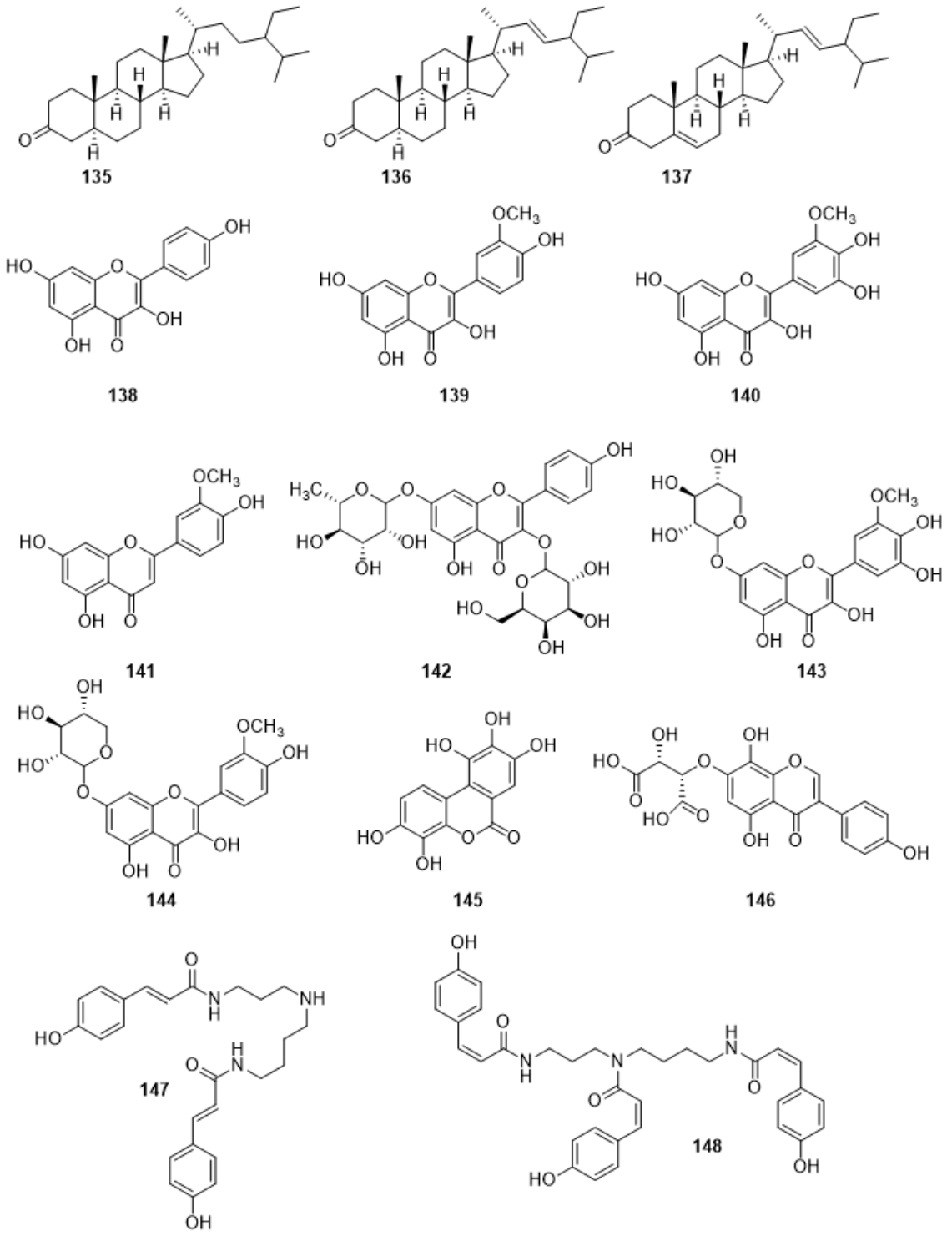


**Fig. (10a).** Bioactive compounds from *N. nouchali.*

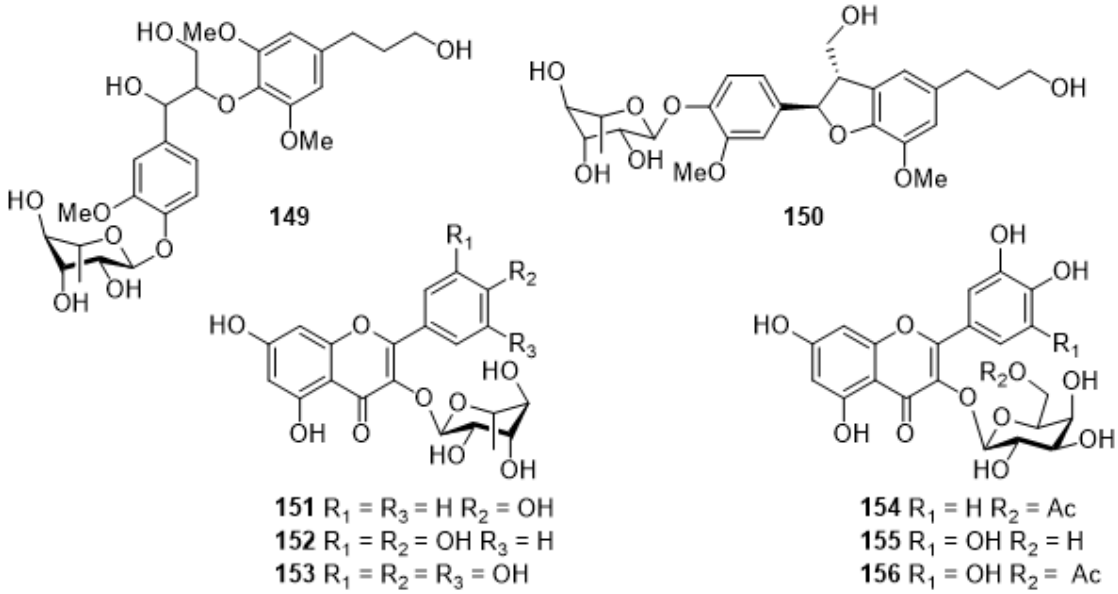


**Fig. (10b).** Bioactive compounds from *Nymphaea odorata.*

A $Ca^{2+}$-dependent novel lectin have been isolated from *Nymphaea nouchali* tuber. The antiproliferative activity of this lectin against EAC (Ehrlich ascites carcinoma) cells showed 56% and 76% inhibition (*in-vivo*) in mice at 1.5 and 3 $mg \cdot kg^{-1} \cdot day^{-1}$ respectively [92]. The ethanolic extract of *N. nouchali* flowers showed antioxidant activity against nitric oxide and hydrogen peroxide in concentration dependent manner with $IC_{50}$ values of 68.39 and 64.54 µg/ml, respectively [93]. The crude extracts of *N. nouchali* and various column fractions exhibited poor antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria and fungi but significant cytotoxic effect in brine shrimp lethality bioassay. Three steroids, namely 24-ethyl-5α-cholestan-3-one (**135**), 5α-stigmast-22-en-3-one (**136**) and stigmast-5,22-dien-3-one (**137**) were isolated from the petroleum ether extract of *N. nouchali* [94]. However, no biological activities were evaluated for these compounds. Apart from this the methanolic extract of *N. nouchali* flowers has shown attenuation of melanogenesis through the regulation of cAMP/CREB/MAPKs/MITF and proteasomal degradation of tyrosinase.

It significantly inhibited the monophenolase and diphenolase activities of mushroom tyrosinase by 94.90±0.003% and 93.034±0.003%, respectively at a concentration of 100 µg/ml. It also suppressed cellular tyrosinase activity significantly and melanin synthesis *in-vitro* in melanoma cells and *in-vivo* in HRM2 hairless mice. Furthermore, it inhibited tyrosinase (TYR), tyrosinase-related protein (TYRP)-1, TYRP-2, and microphthalmia-associated transcription factor (MITF) expression, thereby blocking melanin synthesis. The plant extract suppressed cAMP production with subsequent down regulation of CREB phosphorylation. It stimulated MAP kinase phosphorylation (p38, JNK, and ERK1/2) and the proteasomal debasement pathway, leading to degradation of tyrosinase and MITF and the suppression of melanin production. The active metabolite identified form the plant extract were, kaempferol (**138**), isorhamnetin (**139**), laricitrin (**140**), chrysoeriol (**141**), kaempferol-3-*O*-galactoside-7-*O*-rhamnoside (**142**), laricitrin-7-*O*-xyloside (**143**), isorhamnetin-3-*O*-xyloside (**144**), 3,4,8,9,10-pentahydroxy-dibenzo[b,d]pyran-6-one (**145**), shoyuflavone C (**146**), di-*p*-coumaroylspermidine (**147**) and N1,N5,N10-(Z)-tri-*p*-coumaroylspermidine (**148**) (Fig. 10a) [95].

Two lignans, nymphaeoside A (**149**), icariside E4 (**150**), along with few other flavonoid glycosides, kaempferol 3-*O*-α-L-rhamnopyranoside (afzelin, **151**), quercetin 3-*O*-α-L-rhamnopyranoside (**152**), myricetin 3-*O*-α-L-rhamnopyranoside (myricitrin, **153**), quercetin 3-

*O*-(6"-*O*-acetyl)-β-D-galactopyranoside (**154**), myricetin 3-*O*-β-D-galactopyranoside (**155**), and myricetin 3-*O*-(6"-*O*-acetyl)-β-D-galactopyranoside (**156**) were isolated from alcoholic extract of *Nymphaea odorata* Aiton (Fig. 10b). Of these, compounds **151**, **152** and **155** displayed marginal inhibitory effects against fatty acid synthase inhibition assay with $IC_{50}$ values of 45, 50, and 25 μg/ml [96].

### *2.11. Scirpus maritimus* L.

The root of *Scirpus maritimus* L. has been used as an astringent and as a diuretic in China. However, no chemical compounds have been isolated and tested for their astringent and diuretic activity. Though, few cytotoxic stilbenes namely, viniferin (**157**), scirpusin A (**158**), scirpusin B (**159**), resveratrol (**160**) and piceatannol (**161**) have been isolated from this aquatic plant. The root of the plant has been used in China as an astringent and as a diuretic medicament [97]. Cytotoxic stilbenes such as, combretastatins and its analogues are very popular as tubulin binding agents and active against numerous cancer cell lines. Combretastatin A-4 (**162**) is the most potent naturally occurring combretastatin, which was isolated from the bark of a South African tree *Combretum caffrum* (Fig. 11). Combretastatin A-4 and its analogues are currently under clinical trial for the treatment of cancer [98].

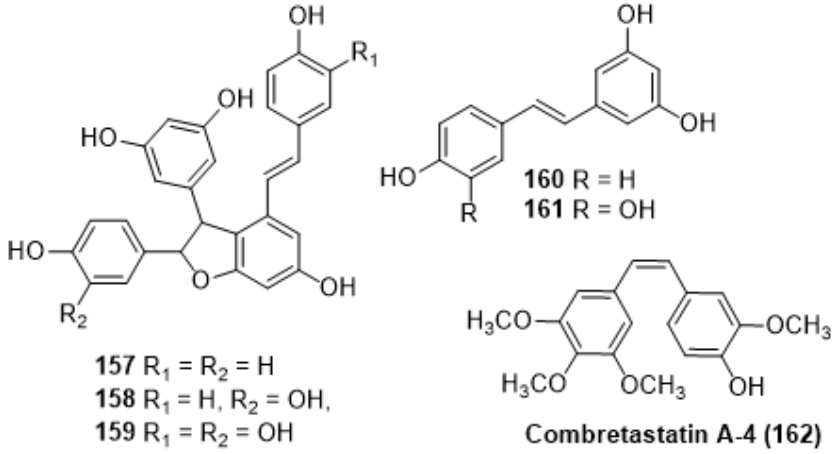


**Fig. (11).** Bioactive compounds from *S. maritimus*.

### *2.12. Zantedeschia aethiopica* (L.) Spreng.

A few antialgal compounds have been isolated *Zantedeschia aethiopica* (Fig. 12) [99]. Of these, the *β*-sitosterol (**163**) and (+)-pinoresinol (**164**) were the major components. A detailed literature search revealed that *β*-sitosterol and two compounds similar to (+)-pinoresinol (**176** and **177**) have shown anti-cancer property against various cancer cell lines [100].

The *β*-sitosterol possessed antiproliferative activity against breast cancer cell line (MCF-7), human leukemic cells (U937) and colon carcinoma cells (HT-29). The *β*-sitosterol containing extracts have also shown anticancer activity against human prostate cancer cell lines (nonmetastatic and metastatic). Two lignans, (+)-epiaschantin (**176**) and (+)-epieudesmin (**177**), (Fig. 12b) which are closely similar to (+)-pinoresinol (**164**) have shown good cytotoxicity against lymphocytic leukemia cells (P388), pancreas adenocarcinoma cells (BXPC-3), breast adenocarcinoma (MCF-7), central nervous system glioblastoma cells (SF268), lung large cells (NCI-H460), colon adenocarcinoma cells (KM20L2) and prostate carcinoma cell line (DU-145) [101]. The other chemical constituents are phenyl propanoids (**165-171**), flavonoid glycosides (**172**, **173**) and neolignans (**174**, **175**).

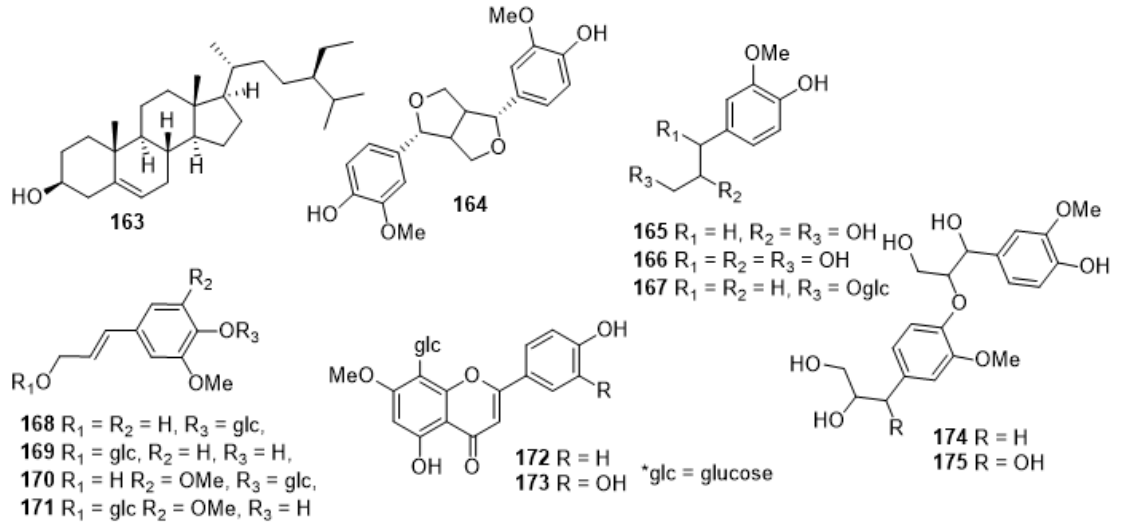


**Fig. 12a**

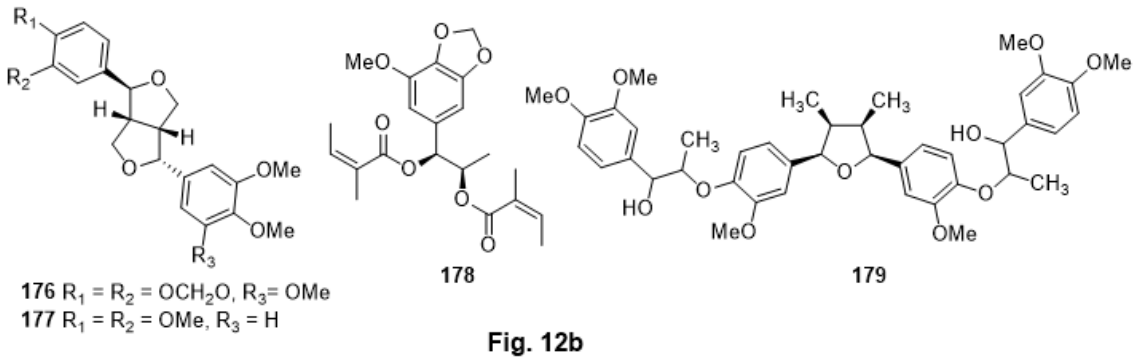


**Fig. 12b**

**Fig. 12. (a)** Chemical constituents of *Z. aethiopica* **(b)** Similar cytotoxic compounds isolated from other plants.

The compounds from these classes such as 2-epilaserine (**178**) and manassantin A (**179**) have been reported to have the cytotoxic properties [102, 103]. Thus, the Z. aethiopica extracts and compounds **165-175** might also be active against the cancer cell lines.

## 4. DISCUSSION

The *A. calamus* has been used as a traditional medicinal for the treatment of several illnesses and have been reported to possess numerous biological activities. However, chemical compounds isolated from the plants have been reported to possess hepatoprotective, anti-seed germination, neuroprotective, anti-obesity, insecticidal and anti-cancer activities only. Hence, a detailed bioassay guided extraction, isolation and identification of bioactive compounds can be done from the different plant parts for the other reported biological activities such as, sedative and hypnotic effect, CNS depressant, anticonvulsant activity, anti-inflammatory, antioxidant, cardiovascular, hypolipidemic, actions on respiratory system, immunosuppressive, antiulcer and cytoprotective, antidiarrheal, antispasmodic, antibacterial, antifungal, antiviral, anthelmintic, piscicidal, adulticidal, diuretic activity and insulin sensitization activities.

Similarly, *C. asiatica* have been reported to possesses antiallergic, anti-pruritic, anti-ulcerogenic, neuroprotective, wound healing, anti-inflammatory, antipsoriatic, hepatoprotective, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial, insecticidal, antifungal, antioxidant, larvicidal

activities and adult emergence inhibitory activity against mosquito *Culex quinquefasciatus* but majority of the compounds isolated from the plants have been evaluated for their neuroprotective effect and cytotoxicity against few elected cancer cell lines only. Hence, the plant can be further explored in terms of bioassay guided extraction, isolation and identification of lead molecules and assessment of their bioactive potential for the validation of its traditional usages and other reported biological activities.

The *C. benghalensis* have shown notable cytotoxic, anti-depressant, sedative, and anxiolytic properties. However, only three steroidal compounds (**56-58**) with antioxidant activity have been isolated from the plant so far. Thus, these compounds can be tested for their cytotoxic, anti-depressant, sedative and anxiolytic properties or other compounds, responsible for these activities can be isolated from different plant parts. The other biological activities and bioactive compounds can also be evaluated and identified for the justification of its traditional usages.

*Crinum* species has been known for its various traditional usages and diverse biological activities. However, most of the isolated compounds (mostly alkaloids) have been reported to possess only few biological activities like antimalarial, immunomodulatory, and cytotoxic activities. Hence, it is worthwhile to test isolated alkaloids for other biological activities and to do detailed bioassay guided isolation of other compounds from aquatic *Crinum* species responsible for other biological activities.

Lycorine (**65**) isolated from *Lycoris radiata* has been reported to exhibit anti-severe acute respiratory syndrome coronavirus (SARS-CoV) activity with a half maximal effective concentration ($EC_{50}$) and selectivity index (SI) value of 15.7 μg/mL and 954, respectively and therefore Verma et. al. 2020 hypothesized that it may inhibit SARS-CoV-2 as well. This hypothesis was further validated by study done by Zhang et al. 2020 to assess the *in-vitro* anti-SARS-CoV-2 potential of lycorine. The result of this study revealed that lycorine significantly inhibits SARS-CoV-2 with an $EC_{50}$ and SI value of 0.3 μM and >129, respectively [104, 105]. Since, lycorine and similar alkaloids have been identified in several *Crinum* species including *C. macowanii* [106], the plant extracts and alkaloid fractions might be significant inhibitor of SARS-CoV-2 and might be very helpful in treatment of COVID-19 through an herbal medication.

*Cyperus rotundus* has also been used traditionally for the treatment of several ailments and has been reported for several biological activities. However, only few antifeedant and cytotoxic furochromones have been isolated from the plants. Apart from this an insecticidal sesquiterpene, nootkatone (**81**) has been isolated which also exhibits antiplatelet effect. Few alkaloids (**82-88**) have also been isolated but not evaluated for any biological properties. Thus, these alkaloids can be evaluated for the other biological activities reported for the plant or other compounds responsible for those activities might also be isolated from the plant. *Gunnera perpensa* extract has been reported to possess cytotoxicity in brine shrimp lethal assay and few cytotoxic compounds (**93** & **96**) have also been isolated from the plants. However, it has been traditionally used for the treatment of venereal diseases, infertility, endometritis, urinary tract problems, impotence, cold, menstrual pain, wounds, and psoriasis etc. Hence, the scientific assessment of these traditional usages must be done by detailed bioassay guided extraction, fractionation, isolation, and identification of chemical constituents.

Resin glycosides have been isolated from the many *Ipomoea* species and have been reported to exhibit moderate cytotoxicity and antibacterial activities. However, these compounds are not as much explored with respect to the biological activities as the alkaloids. Hence, the resin glycosides can be further evaluated for the other biological activities like the alkaloids of these plants. One of the alkaloids, swainsonine (**101**) is a very important compound as it reduces the human gastric carcinoma [137]. In phase I clinical trial it has shown to reduce both rate of tumor growth, and metastasis [138,139]. However, no evidence of anti-tumor activity of swainsonine was seen in phase II clinical trial, in patients with locally advanced or metastatic renal cell carcinoma [140].

Similarly, *Juncus* species have been reported to possess several biological activities such as cytotoxicity antioxidant, hepatoprotective, antiviral, antimicrobial, anti-algal, anti-inflammatory, and anti-eczematic activities and few chemical constituents having similar activities have also been identified. However, there are many more similar compounds isolated from these species which are yet to be evaluated for their biological potential.

*Mentha longifolia* has been used traditionally against several ailments like constipation, fever, nausea, bronchitis, common cold, cough, peptic and intestinal ulcer, general weakness, wound healing, inflammation, and liver disorders etc. However, only three flavonoid glycosides (**132-134**) with moderate cytotoxicity have been isolated from the plant. Hence, a detailed bioassay guided extraction and isolation is needed to explore its complete biological potential. *Nymphaea nouchali* extract has shown significant activities like antidiabetic, hepatoprotective, antiproliferative, mutagenic, antitumor, cholinergic, analgesic, anti-inflammatory, antimicrobial activity, antinociceptive, antioxidant, anti-urolithiatic activity and uterotonic activities and number of chemical constituents including, alkaloids, flavonoids, steroids, and terpenes have been isolated from the plants [107]. However, the detailed bioassay guided isolation and identification of active compounds against individual disease is still to be done.

*Scirpus maritimus* is used as an astringent and a diuretic herbal medicine in China but only few cytotoxic stilbenes (**157-161**) have been isolated form the plants. Hence, a detailed study needs to be done for the assessment of its diuretic potential and toxicity of the plants and active metabolites. One lignin (**164**) along with other phenolic compounds and *β*-sitosterol have been isolated form *Zantedeschia aethiopica* and *β*-sitosterol has been reported to possess antiproliferative activity against breast cancer cell line (MCF-7), human leukemic cells (U937) and colon carcinoma cells (HT-29). However, this lignan has not been evaluated for its biological properties despite the similar lignans (**176** and **177**) have been reported to exhibit remarkable cytotoxic activities. Similarly, the phenyl propanoids (**165-167**) and neolignans (**174** and **175**) have not been evaluated for their biological properties whereas similar compounds **178** and **179**, have been reported to exhibit remarkable cytotoxicity. Hence, a detailed bioassay guided isolation and identification of the cytotoxic compounds from this plant is much needed.

Thus, considering the therapeutic applications of aquatic plants, the conservation of the wetlands and aquatic plants is much needed. The possible reason behind the extinction of the aquatic plants and degradation of the wetlands is the lack of knowledge in less educated population about the therapeutic benefits of aquatic plants, the conservation status, and legislative regulations regarding the harvesting of the threatened, endangered and red listed plants and apathy of the educated youth population towards the natural resources. Hence, the following steps need to be followed to save the South African wetland biodiversity,

- To provide complete information about the socio-economic and therapeutic importance of the wetland resources and to motivate the youth to take interest into the uses and benefits of the wetland resources, legislative regulations regarding the estimates of the threatened, endangered, and red listed plants and its conservation.
- To improve environmental awareness on resource management by interacting with rural people through different awareness programs.
- To motivate the people to enhance participation in these programs to enhance mechanisms for wetland conservation.
- To introduce traditional mechanisms to wetland management enforced by traditional leaders.
- To introduce basic environmental management studied on all fields of tertiary studies as they all interlink to the environmental systems.

## CONCLUSION

The aquatic plants have been used by traditional healers for the treatment of several diseases. The rural communities are still using the wetland resources for their cultural, medicinal, economic, domestic, and agricultural needs. Various plants including some listed threatened and protected plant species are being collected for medicinal purposes. However, due to continuous increase in population, carelessness, and unawareness about the therapeutic benefits of aquatic plants, the conservation status and legislative regulations regarding the harvesting of the threatened, endangered and red listed plants, several plant species are getting extinct and most of the non-protected wetlands are getting degraded and transformed for agricultural practice. However, the aquatic plants are a great source of diverse varieties of bioactive secondary metabolites including terpenes, steroids, alkaloids, resin glycosides, dihydrophenanthrenes, stilbenes, lignans, phenolics and flavonoids. The plant extracts and the isolated compounds possesses diverse biological activities like neuroprotective, antimalarial, anticancer, antioxidant, antibacterial, anti-inflammatory, immunomodulatory, antimetastatic, phytotoxic, psychotropic, psychotomimetic, and anti-COVID-19 activities. Thus, the protection and cultivation of aquatic plants and wetland is an urgent need of the hour. However, these plants need to be explored further, regarding their medicinal properties, bioactive compounds, and scientific validation of their traditional usages.

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.


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