Chapter 6

Pharmacological Activities of Cyperaceae Members

Abstract

Cyperaceae species include widely used medicinal plants across the world, and numerous experimental evaluations have scientifically validated the pharmacological activities of Cyperaceae plants along with the identification of active compounds, especially of the most important species, *Cyperus rotundus.* However, still most of the Cyperaceae members are considered as problematic weeds, and translation of the research findings to value added products is the need of the hour, and several attempts have been initiated in this regard. The major pharmacological properties of the Cyperaceae species are updated in the chapter, of which antimicrobial, anti-inflammatory, antioxidant, anticancer, anti-obesity, oral hygiene and wound-healing activities are the prominent ones. The pharmacological properties of the major isolated compounds from Cyperaceae species are also discussed in the chapter.

Introduction

Most of the modern medicines can be traced back to traditional medicinal plants, where the scientific validation of the traditional information using modern scientific tools has led to the discovery of bioactive molecules as drugs (Petrovska, 2012). The diversity of secondary metabolites is immense in medicinal plants, and therefore the pharmacological assays also need to be diverse to assess the activities of the compounds. Basically, the assays can be either cell-free (biochemical) or cell-based procedures. The wide range of bioassay approaches such as bio-guided fractionation, micro-fractionation bioactivity-integrated fingerprint, HPLC biochemical detection, biochromatography and electrophoretic enzyme assays enables rapid screening and identification of compounds from complex mixtures.

Though the pharmacological activities of *Cyperus rotundus*, the most important Cyperaceae member, have been reviewed extensively, a comprehensive review of the pharmacological efficacy of other Cyperaceae members is rare (Bajpay *et al.*, 2018). The present chapter elaborates the pharmacological properties of the crude extracts and isolated

pure compounds from Cyperaceae members (**Figure 1**). The general therapeutic activities are elaborated first, followed by the potential applications of isolated compounds from various Cyperaceae plants. Among the various therapeutic potentials attributed for Cyperaceae plants,antibacterial, antiviral, anti-inflammatory, antioxidant, anticancer, antiulcer, analgesic, antiarthritic, antipyretic, wound healing, hepatoprotective, anti-obesity, antidepressant, anti-androgenic,anticonvulsant, antidiarrheal, antigenotoxic, neuroprotective, nootropic, anti-dysmenorrhea and antiparasitic activities are discussed in detail.

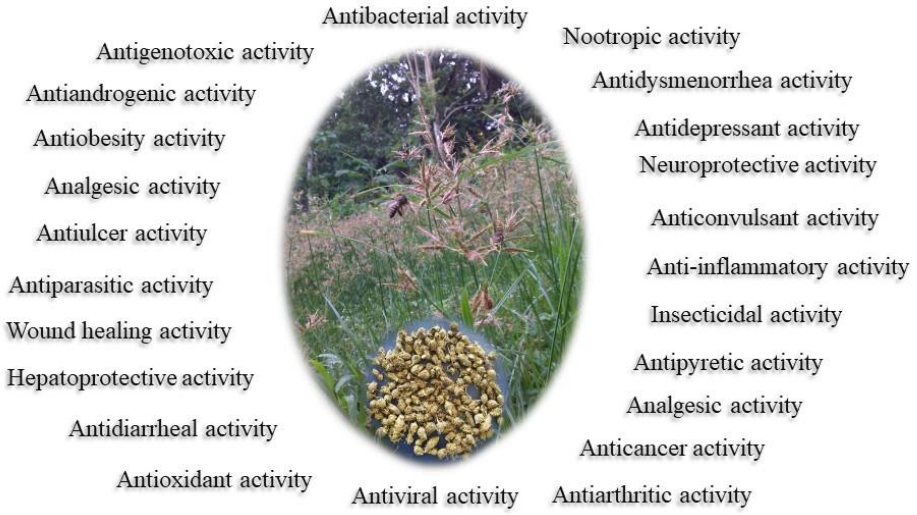

Figure 1. Pharmacological activities reported for Cyperaceae members

Antibacterial activity

Bacteria are the most common reason of infectious diseases and can be treated with antibiotics.Resistance to antibiotic agent is emerging in a wide variety of pathogens and multiple drug resistance is becoming common in differentbacterial strains. Plant based drugs play a major role in curing bacterial infections and there have been a lot of investigations of plants as sources of antibacterial agents, especially against drug resistant strains, and several Cyperaceae members also have been investigated in this direction (Karamolah *et al*., 2017). Essential oils, solvent extracts and isolated pure compounds of the plant group have been investigated in detail.

The essential oils and extracts of various *Cyperus* species are reported to possess antibacterial activity on both Gram-positive and Gram-negative bacterial strains.The phytochemicals in *Cyperus rotundus* showed antibacterial activity against several food borne pathogens, and the ability of *Cyperus rotundus* to inhibit *Streptococcus mutans* may have contributed to the low level of dental caries in certain prehistoric populations (Buckley *et al*., 2014). The essential oil components of *Cyprus rotundus* exhibited strong antibacterial activity against *Streptococcus aureus* (Liang *et al*., 2017). *Cyperus kyllinga* oil exhibited high activity against *Streptococcus aureus* and moderate activity against *Escherichia coli*, *Pseudomonas aeruginosa, Aspergillus flavus* and *Candida albicans* (Khamsan *et al.,* 2011). The antibacterial activity of *Cyprus papyrus* oil was assayed using agardisc diffusion and brothmicro dilution methods. The MIC values revealed that the oil samples inhibited the growth of *Streptococcus aureus*, *Escherichia faecalis* and *Escherichia coli* significantly (Lawal *et al*., 2016). Swamy *et al.* (2016) reported *Cyperus longus* essential oil as effective against the food-borne pathogens *Streptococcus aureus, Listeria monocytogenes, Escherichia faecium, Streptococcusenteritidis, Escherichia coli* and *Pseudomonas aeruginosa.*

Various extracts of *Cyperus rotundus* were evaluated for antibacterial activity against both Gram-positive and Gram-negative bacteria and found to be highly effective. The activities were also evaluated against numerous clinical isolates and the major observation was that the ethanol extract exhibited highest activity. The methanol extract of the plant *Cyperus conglomerates* showed activity against both Gram-positive and Gram-negative bacterial strains (Hisham *et al.,* 2012). Ethanol extract of *Cyperus esculentus* possess activity against different bacterial strains including *Staphylococcusaureus, Bacillus subtilis, Escherichia coli* and *Enterococcus faecalis* (Dimayuga *et al.,* 1998). Dini *et al.* (1992) reported that *Cyperus incompletes* possess weak activity against various Gram-positive and Gram-negative bacteria strain. Ethanol extract of *Cyperus scariosus* showed strong activity against *Staphylococcus aureus* strain but found to be inactive against various other bacterial strains (Lahariya, 1979). The methylene chloride extract of the rhizomes of *Cyperus sphacelatus* showed anti salmonella activity (Mfonku *et al*., 2021).

Along with the *Cyperus* species, other members of the Cyperaceae family also showed remarkable antibacterial activities. *Scleria striatinux* is one among the most active African

botanicals against *Helicobacter pylori* infections (Nayim *et al.*, 2022). Antibacterial activity of the crude extract of *Scleria striatinux* supports their use in traditional medicine (Mbah *et al.*, 2012). Ethyl acetate extract of *Scirpus holoschoenus* showed anti-bacterial effect against *Staphylococcus aureus* and *Bacillus subtilis* with MIC values 0.4 and 0.6 µg/mL respectively (Saliha *et al*., 2017). *Carex* species are reported to have activity against various bacterial strains. *Carex cruciata, Carex alopecuroides* and *Carex baccans* exhibited antibacterial activities (Bogucka-Kocka *et al*., 2011). *Carex humilis* extract has been identified as an active ingredient in an anti-microbial composition and is harmless to the human body and has no side effects (Seo, 2015). In the discdiffusion antimicrobial assay, the crude extract of *Fimbristylis aphylla* produced moderate to strong antimicrobial activity against the test organisms and the strongest zone of inhibition was found against *Shigella dysenteriae* (Islam *et al*., 2011). The dichloromethane-methanol (1:1) extract of the whole plant of *Rhynchospora corymbosa* exhibited variable MICs and significant antimicrobial activity (Pagning *et al*., 2016).

Oral hygiene

Cyperus rotundus extract can be considered as a suitable candidate for the treatment and prevention of periodontitis and tooth decay, and the tubers have traditionally been used for oral hygiene in various cultures across the globe (Khojaste *et al*., 2018). The microbes *Streptococcus mutans, Aggregatibacter actinomycetemcomitans* and *Candida albicans* have major roles in damaging oral hygiene. Among the various solvent extracts, alcoholic extract of *Cyperus rotundus* had the greatest effect on the inhibition of growth of *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans* (Khojaste *et al*., 2018). The adherence of *S. mutans* to salivacoated hydroxyapatite beads was completely inhibited at the concentration of 4 mg/ml of the tuber extract of *Cyperus rotundus* (Yu *et al*., 2007). *Cyperus rotundus* root extract effectively increased the expressionof TGF-β1, triggered migration and increased the proliferation of fibroblasts, which ultimately increased the quantity of fibroblasts in the wound area of the oral mucosa traumatic ulcer in Wistar rats (Berniyanti *et al*., 2019). An extractive of *Cyperus rotundus* has been indicated as an active mouthwash (Abbas *et al*., 2019). Further, patent search reveals different kinds of oral

hygiene products from *Cyperus rotundus* tuber extracts such as mouth wash, tooth paste,tooth powder andthroat lozenge.

Antiviral activity

Viral infections commonly include respiratory infections, digestive system infections, viral haemorrhagic fevers, sexually transmitted infections, neurological infections and congenital infections. Traditional medicines use a multitude of medicinal plants and formulations that shows antiviral activity and may be of benefit in treating emerging viral diseases including COVID 19. Antiviral activity, as measured by inhibitory effects of viral replication in cell culture, has commonly been used to evaluate *in vitro* pharmacologic activity of plant extracts and isolated compounds (Samuel, 2001).

Cyperaceae species are reported as good source of antiviral agents. *Cyperus rotundus* extracts exerted virucidal effect against HS, HB, hepatitis A, hepatitis B, Coxsackie and herpes simplex type 1 viruses (Soltan and Zaki, 2009; Parvez *et al*., 2019; Xu *et al*., 2020). However, the rhizome essential oil showed only negligible activity against hepatitis A, herpes simplex type 1, and coxsackie viruses with percent protection 7.9, 14.2 and 8.7 %, respectively (Samra *et al*., 2020). A recent study has proved that the green synthesized silver nanoparticles of *Cyperus rotundus* could have antiviral activity against infectious laryngotracheitis virus (ILTV) and infectious bronchitis virus (IBV) in chickens (Abo-El-Yazid *et al*., 2022). *Cyperus niveus*ethanol extract showed antiviral activity against Ranikhet virus. *Cyperus pangorei* ethanol-water extract showed antiviral activity against *Vaccinia* and *Ranikhet* viruses.

Coronavirus disease 2019 (COVID-19) is a viral respiratory disease that has spread across the globe recently as a pandemic. The treatment of COVID-19 has been hampered due to the lack of effective therapeutic efforts. Main Protease (M^{pro}) is a key enzyme in the viral replication cycle and its non-specificity to human protease makes it a potential drug target. *Cyperus rotundus*, which belongs to the Cyperaceae family, is a traditional herbal medicine that has been widely studied for its antiviral properties. The plants as well as isolated compounds are reported as potential against SARS CoV-2 (Khuntia *et al*., 2021). On docking analysis, it has been observed that the phytochemicals α-cyperone and patchoulane derivatives possess excellent inhibitory activity against proteins of SARS CoV-2 virus

(Vincent *et al.,* 2020). Sugetriol-3,9-diacetate from *Cyperus rotundus* exhibited high binding affinity to PL^{pro} of SARS CoV-2, suggesting the utility of this plant in the treatment of SARS-CoV-2 (Wu *et al*., 2020; Birendra Kumar *et al*., 2021).

Anti-inflammatory activity

Inflammation is a process by which the body's white cells protect the body from outside invaders such as bacteria and viruses. Inflammation can be either short lived (acute) or long-lasting (chronic). Conditions linked to chronic inflammation include cancer, heart disease, diabetes, asthma and Alzheimer's disease. Medicinal plants, their extracts and isolated compounds are always interesting targets for anti-inflammatory drug development (Ghasemian *et al*., 2016).

Species of the family Cyperaceae are used in traditional medicine in several countries for the treatment of some illness that have associated inflammatory complications. The anti-inflammatory action of the extract from *Cyperus rotundus* rhizome was first described in 1971 by Gupta *et al*., and since then investigations have been ongoing to understand the anti-inflammatory effect of different extracts or active constituents of *C. rotundus*. The phytochemicals found in *C. rotundus* oil were found to inhibit lipopolysaccharide (LPS) stimulated inflammatory response in a murine BV-2 microglial cell line and suppressing the nuclear factor kappa light chain enhancer of the activated B cell (NF-κB) pathway (Huang *et al*., 2018). Moreover, recent evidence has shown that the topical application of *C. rotundus* rhizome extract in a rat model with chronic and acute dermatitis lead to a reduction in ear oedema and inflammatory cell infiltration generated by exposure to 12-O-tetradecanoylforbol-acetate (TPA). This ultimately suggested that the extract could be a potential therapeutic tool for the treatment of inflammatory skin disorders (Rocha *et al.,* 2020). The compounds nootkatone, α-cyperone, β-selinene and valencene contribute to anti-inflammatory activity through their action on hemeoxygenase-1 pathway (Khan *et al*., 2011; Tsoyi *et al.,* 2011). The ethanol extract as well as volatile compounds of *Cyperus rotundus* were antiallergic both *in vivo* and *in vitro* by inhibiting the production of leukotrienes and B-hexosaminidase in basophilic leukemia cells of rat (Jin *et al.,* 2011). Mardiana *et al*. (2020) studied the activity of *Cyperus rotundus* against psoriasis and found that the plant has the potential of repairing the skin.

Various extracts of *Cyperus iria* are reported to possess anti-inflammatory activity. Vera *et al*. (2022) showed the anti-inflammatory activity of the ethanol extract of *Cyperus iria. Cyperus conglomeratus* extract exerted promising anti-inflammatory actions *via* suppressing the serum levels of TNF-α and galactin-3 in a dose-dependent manner (El-Shamy *et al*., 2020). *Scirpus* is an important genus in Cyperaceae with potent anti-inflammatory effects. *Scirpus yagara* tubers have long been used as traditional Chinese medicine. Li *et al*. (2014) reported the anti-inflammatory activity of the tubers of *Scirpus yagara* both *in vitro* and *in vivo*. *Fimbristylis aestivalis* is proved as a potential source of cyclooxygenase-2 (COX-2) inhibitors. The methanol extract of *Carex humilis* has anti-inflammatory activity against the prostaglandin H2 synthase (Lee *et al*., 1998). *Carex cruciata, C. alopecuroides* and *C. baccans* exhibited anti-inflammatory activities (Bogucka-Kocka *et al*., 2011).

Antioxidant activity

Oxidative stress is an important risk factor in the pathogenesis of numerous chronic diseases. Free radicals and other reactive oxygen species are recognized as agents involved in the pathogenesis of ailments such as asthma, inflammatory arthropathies, diabetes, Parkinson'sdisease, Alzheimer's disease, atherosclerosis as well as various types of cancers. Reactive oxygen species are also said to be responsible for the human aging. Antioxidants are compounds that inhibit oxidation, a chemical reaction that can produce free radicals. Plants are considered as good antioxidants, and plant phenolic acids, poly phenols and flavonoids trap free radicals such as peroxide, hydroperoxide or lipid peroxides and thus inhibit the oxidative mechanisms that lead to degenerative diseases (Wu *et al*., 2011).

Cyperaceae members are well known for its antioxidant potential. *Cyperus, Remirea, Rhynchospora* and *Scleria* and are the major genus in Cyperaceae family with antioxidant activity. Among these, *Cyperus* species received much attention. *Cyperus rotundus* was found to be a natural antioxidant and a free radical terminator (Kilani *et al*., 2008). Jihan *et al*., 2021 observed that *Cyprus rotundus* act as a protective agent against oxidative stress, neurotoxicity and inflammation induced by esfenvalerate. The flavonoids in the methanol extract of *Cyperus rotundus* significantly inhibited lipoperoxidation by maintaining the live antioxidative defense system, in addition to ROS and NO scavenging, and ultimately

reducing the activities of transaminases and alkaline phosphatase as well as the levels of glucose and bilirubin in the blood serum.

Rakotonirina *et al*. (2001) observed that the methanol extract of *Cyperus articulates* showed antioxidant activity with IC_{50} 171.8 µg/ml. The essential oils of *Cyperus articulates* rhizome encapsulated in chitosan nanoparticles revealed a high potential to eliminate free radicals. The encapsulation improves the stability and also the efficiency of extracts of *Cyperus* spp. (Kavaz *et al.,* 2019). Hot water extract of *Cyperus esculentus* possess antioxidant activity (Cook *et al*., 1998). The milk extracted from *Cyperus esculentus* tubers increased the activity of antioxidant enzyme superoxide dismutase (SOD), while malondialdehyde concentrations were lowered compared to the control group, thus demonstrating good antioxidant activity (Onuoha *et al*., 2017). Ethanol and n-hexane extracts of *Cyperus esculentus* showed superior antioxidant activity (Nwosu *et al*., 2022). Antioxidant activity of the volatile oil of *Cyperus alternifolius* was tested using DPPH free radical assay and found to exhibit significant antioxidant activity (Ahmed, 2012). *Cyperus compressus* is an excellent source of antioxidant-based phytonutrients, validating its traditional use (Datta *et al*., 2018). An experiment, assessing the antioxidant activity of the extracts of *Cyperus tegetum* demonstrated significant DPPH radical, superoxide anion and hydrogen peroxide scavengingactivities compared to the standards, such ashydroxybutylanisol, butylhydroxytoluene and ascorbic acid (Chatterjee and Khanra, 2019). Alif *et al*. (2018) reported the antioxidant potential of *Cyperus odoratus*.

The ethyl acetate fraction of *Scirpus holoschoneus* showed highest antioxidant activity among various species tested (Saliha *et al*., 2017). The methanolic extracts of seeds of *Scirpus articulates* showed good antioxidant potential in ABTS assay (Bhardwaj *et al*., 2014). The methanol extract of *Fimbristylis miliacea* and *Fimbristylis dichotoma* showed significant antioxidant activity (Ramli *et al.*, 2022). The novel feruloyl monoglyceride macrocycles isolated from the leaves of *Carex distachya* displayed strong antioxidant activity against reactive oxygen species and inhibited malondialdehyde synthesis (Fiorentino *et al*., 2007). The IC_{50} of the root methanol extract of *Carex distachya* was 4.2 µg/mL for DPPH radical scavenging assay, and the resveratrol derivatives, lignans and

phenylethanoids were identified as the responsible compounds for the antioxidant activity (Fiorentino *et al*., 2008).

Anticancer activity

Despite the developments in understanding the mechanism of cancer cells and treatments, the ailment remains uncurable to a large extent, and the situation demands for an alternative treatment solution (Gilbert, 2000). Herbal medicine provides a feasible alternative to western medicine against cancer, and in fact most of the chemotherapeutic drugs for cancer treatment are molecules identified and isolated from plants or their synthetic derivatives.Plants play an important role in anticancer treatment through regulating signalling pathways. The main mechanism of anticancer activity of plant extracts is by inhibiting the cell proliferation or by inducing apoptosis in the cancerous cells.

The anticancer activity of *Cyperus rotundus* extracts has been assessed, and the mechanism of action also elucidated. Human cervical cancer (HeLa) cell lines exposed to different doses of *Cyperus rotundus* extracts revealed morphological modifications and changes in the degree of chromatin condensation. *Cyperus rotundus* ethanol extracts were used to evaluate its effects on triple-negative breast cancer cells (TNBC) (negative for estrogen, progesterone receptors, and human epidermal growth factor receptor 2 (HER2) protein over expression). The extracts inhibited the TNBC cell proliferation, which might be related to cell cycle arrest at the G0/G1 phase, thus inducing apoptosis by promoting Bcl-2associated X protein (Bax) expression and inhibiting B cell lymphoma (Bcl) expression. The n-hexane extract from *Cyperus rotundus* rhizomes showed activity on MCF-7 breast cancer cell lines, by inducing apoptosis and halting them in G0-G1 stages of the cell cycle (Simorangkir *et al*., 2019). Samra *et al*. (2021) studied the petroleum ether and methylene chloride extracts of *Cyperus rotundus* and reported remarkable cytotoxic activity against the HepG2. The phenolic compounds in *Cyperus rotundus* were found to be significant antiproliferative agents, and arrest the cell cycle, inhibit DNA binding, regulate carcinogenic metabolism and ontogenesis expression, prevent cell adhesion, migration, and differentiation, and block signal pathways to induce apoptosis (Huang *et al*., 2020). Both the ethanolic and methanolic extracts showed higher antiproliferative activity associated

with apoptosis induction through upregulation of death receptor 4 (DR4), DR5, and BAX (Park et al., 2014). Various extracts of aerial parts of *Cyperus rotundus* were assayed by *Salmonella typhimurium* assay system and found to possess antimutagenic activity. *Cyperus rotundus* essential oils showed promising level of inhibition on Ehrlich ascites carcinoma cells while on human brain tumor cell lines U 251 and Hela, the activity was negligible (Bisht *et al.*,2011). *Cyperus rotundus* rhizome was found to inhibit cell growth in ovarian cancer cell lines A2780, SKOV3 and OVCAR3. It was observed that the sesquiterpenoid from the plant induces caspase dependent apoptosis in human ovarian cancer cells (Ahn *et al.,* 2015). Wang *et al.* (2021) isolated novel sesquiterpenoids from *Cyperus rotundus* that exhibited inhibitory activity on NF-κB pathway. The petroleum ether fraction of *Cyperus rotundus* rhizome was found to be active against HepG2, PC3 and MCF-7 cell lines using MTT assay and the isolated ceramides from the fraction showed promising anticancer activity (Samra *et al*., 2021).

The anticancer activity of *Cyperus conglomeratus* extracts was tested using silver nanoparticles in MCF-7 breast cancer cells and normal fibroblasts using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), and a selective cytotoxicity against MCF-7 was observed, while in fibroblasts, no toxic effect was reported (Al-Nuairi *et al*., 2020). Methanol extract of the rhizome of *Cyperus tegetum* on MTT assay on Hela cell line showed IC_{50} for the extract at 300µg/mL (Chatterjee *et al.*, 2022). The ethanol extract of *Cyperus exaltatus* exhibited cell cycle dysregulation, ERK1/2/p38 MAPK/AKT phosphorylation, and reduced MMP-9-mediated metastatic capacity in prostate cancer models *in vitro* and *in vivo* (Kim *et al.,* 2022). Phytochemicals in *Carex folliculata* and *Carex gynandra* inhibited the growth of human colon tumorigenic cells mediated by cell cycle arrest, indicating its anticancer potential (Sarrias *et al*., 2011). *Carex cruciata, Carex alopecuroides* and *Carex baccans* also exhibited antiproliferative activities (Bogucka-Kocka *et al*., 2011).

Anti ulcer activity

Gastric ulcer is a prevalent gastrointestinal multi-etiological disorder. Ulcer can be developed inside the inner lining of the stomach (gastric ulcer) or the small intestine (duodenal ulcer). Both the ulcers are also cumulatively referred as peptic ulcers. It affects

nearly 10% of world population. The conventional drugs used in the treatment of ulcer include histamine receptor antagonists, prostaglandins analogues, proton pump inhibitors, cytoprotective agents, antacids and anticholinergics, but most of these drugs produce undesirable side effects or drug interactions and may even alter biochemical mechanisms of the body upon chronic usage. Hence, herbal medicines are generally suggested in such chronic cases, wherein drugs are required to be used for long periods (Bandyopadhyay *et al*., 2002).

The petroleum ether and methanol extracts of *Cyperus rotundus* showed antiulcer activity. **(**Rahman *et al*.1986; Daswani *et al*., 2001). Ethyl acetate fractions of tubers and aerial parts from *Cyperus alternifolius* showed significant antiulcer activity (Farrag *et al.,* 2019). The antiulcer activity of *Cyperus conglomeratus* was confirmed by histopathological, histochemical examinations as evidenced by amelioration of inflammation and preservation of the gastric mucosa against ethanol deleterious effects. The results suggest *Cyperus conglomeratus*as a promising gastroprotective natural remedy and can be incorporated in nutraceuticals (El Shamy *et al*., 2020).

Anti diabetic activity

Diabetes mellitus is one of the common metabolic disorders affecting around 2.8% of the world's population and is anticipated to cross 5.4% by the year 2025. The ailment has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides and glinides. Many of them have a number of serious adverse effects; therefore, the search for more effective and safer hypoglycemic agents is one of the important areas of investigation. One of the promising bio activities of *Cyperus rotundus* is its antidiabetic activity, and it has been used from ancient time to treat hyperglycemic disorders such as diabetes. Administration of *Cyperus rotundus* extract in rats with hyperglycemia lowered their blood glucose level significantly (Raut and Gaikwad, 2006). The aqueous-ethanol fractions of *Cyperus rotundus* showed significantantidiabetic activity, and the phytochemicals of *Cyperus rotundus* have promisingrole in preventing glucose-induced cataractogenesis, visual

impairment, orclouding of eye lens which result from diabetes (Ramya *et al.*, 2012; Rautand Gaikwad, 2012). Methanol extract of rhizomes of *Cyperus tegetum* exhibited significant anti-hyperglycemic activities in alloxan-induced diabetic rats (Chaulya *et al*., 2011). Sudipta *et al*. (2011) investigated the anti-diabetic activity of *Cyperus kyllinga* and concluded that polar part of the plant extract possesses the capacity to reduce the fasting blood sugar and this ability might be due to the reduced insulin secretion in the body.

Analgesic activity

Analgesics relieve pain by acting in the CNS and peripheral pain mediators without changing consciousness. Strong analgesics are more likely to cause side effects such as dependence, addiction and withdrawal symptoms (Mustaffa *et al.*, 2010). Use of medicinal plants is one of the most primary ways of fighting diseases and relieving pain, and plant extracts possessed peripheral analgesic activity and central pain inhibition potential (Parsaei *et al.*, 2016).

One of the major pharmacological activities of the *Cyperus* species is the painrelieving potential. The ethanol extract of *Cyperus rotundus* showed significant analgesic activity by tailflick method on mice (Imam *et al*., 2014). The phytochemicals cyperene and β-caryophyllene oxide in the rhizome essential oil of *Cypeus rotundus* showed excellent analgesic activity in acetic acid induced mice stretching model (Chen *et al.*, 2011). The rhizome essential oil of *Cyperus eleusinoides*showed strong analgesic activity (Kokate and Varma, 1982) The ethanol extract of *Cyperus odoratus* produced analgesic activity due to the inhibition of prostaglandin synthesis by blocking of lipooxygenase and cyclooxygenase activities, and showed a comparable writhing inhibition to diclofenac, the standard analgesic drug (Alif *et al*., 2018).

Anti arthritic activity

The anti-arthritic activity is mainly effected by decreasing the activity of membrane marker enzymes such as alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and by the prevention of leucocytes migration in the inflamed area. Traditional medicinal plants are practiced worldwide for treatment of arthritis especially in developing countries where resources are meagre to access the modern medicines. The anti arthritic activity of *Cyperus rotundus* essential oils

were evaluated and results showed dose dependent antiarthritic activity. Treatment with *Cyperus rotundus* significantly reduced the swelling in the injected area as compared to reference standard. The essential oil of *Cyperus eleusinoides* showed hypothermic effect (Kokate and Varma, 1982).

Antipyretic activity

Antipyretics are the agents which reduce the elevated body temperature. Many plants are being traditionally used in the treatment of fever and their antipyretic activities have been confirmed scientifically (Sultana *et al.,* 2015). The alcoholic extract of *Cyperus rotundus* showed significant antipyretic activity against pyrexia induced in rats, and the active ingredients nootkatone and valencene were confirmed as having antipyretic activity in sepsis animal model *in vivo* (Pal *et al*., 2009). Methanol extract of leaves of *Fimbristylis miliacea* showed antipyretic activity in mice model (Roy *et al*., 2019).

Wound healing activity

Wound healing refers to a living organism's replacement of destroyed or damaged tissue by newly produced tissue. In undamaged skin, the epidermis and dermis form a protective barrier against the external environment. After injury, an inflammation response occurs and there are three stages to the process of wound healing: inflammation, proliferation and remodeling (Garg *et al*., 2011). The wound healing efficacy of various plant extracts have been studied in detail and several plants have been reported with accelerated wound healing activity (Garg and Paliwal, 2011).

The alcoholic extract of *Cyperus rotundus* rhizomes showed considerable variation in wound closure time and tensile strength in different wound models as compared to standard drug nitrofurazone (Puratchikody *et al.,* 2006). An alcoholic extract of the tuber of *Cyperus rotundus* showed wound healing activity in different types of wounds compared with the standard drug nitrofurazone (Imam *et al.,* 2014). Decoction of *Cyperus articulatus* is found to be effective in treating wounds (Mongelli *et al*., 1995).

Hepatoprotectiveactivity

The liver performs a vital role in metabolism, secretion, storage and detoxification of endogenous and exogenous substances. Oxidative stress and free radicals enhance the

severity of hepatic damage, which can be overcome by the antioxidant mechanism. In spite of the scientific advancement in the field of hepatology during recent years, liver problems are on the rise. Only a few drugs are available for the treatment of liver, and in view of the undesirable side effects of the synthetic agents, there is growing demand for the therapeutic evaluation of medicinal plants using systematic research methodology.

Cyperaceae species are reported to exhibit hepatoprotective activity. The ethyl acetate extract of *Cyperus rotundus* was found effective against CCl_4-induced hepatotoxicity in rats (Sureshkumar and Mishra, 2005). Parvez *et al*. (2019), reported the hepatoprotective and hepatic CYP450 enzyme (CYP3A4) modulatory potential of *Cyperus rotundus*. Further, the hexane fraction of *Cyperus rotundus* rhizome reduced the elevated transcription levels of sterol regulatory element binding protein-1c (SREBP-1c) in primary hepatocytes following exposure to the liver X receptor α (LXRα) agonist and ameliorated fatty liver disease and reduced the expression levels of hepatic lipogenic genes in high sucrose diet fed mice. The results suggested that the hexane fraction of *Cyperus rotundus* might be an effective therapeutic agent for fatty liver disease (Yoon *et al*., 2015). *Cyperus alternifolius* showed significant hepatoprotective activity against CCl_4 induced hepatotoxicity in rats (Awaad *et al.*, 2012). *Carex cruciata, C. alopecuroides* and *C. baccans* also exhibited hepatoprotective activity (Bogucka-Kocka *et al*., 2011).

Anti obesity activity

Obesity has become an epidemic worldwide that increase the risk of other diseases like diabetes, cardiovascular diseases and fatty liver disease. It is a complex disease involving an excessive amount of body fat. Usually obesity results from inherited, physiological and environmental factors, combined with diet, physical activity and exercise. Anti-obesity drug act through several potential mechanisms including increased energy expenditure, appetite suppression, inhibition of digestive enzymes or interference in the absorption of fat or sugar from food at the intestinal tract (Muller *et al*., 2022).

Various plant extracts act as potent anti-obesity agents (Fathima *et al*., 2019). Majeed *et al*. (2022) studied the anti-obesity potential of *Cyperus rotundus* hexane extract and showed a reduction in body weight with significant decrease in waist circumference and Body Mass Index. *Cyperus rotundus* hexane extract showed a dose-dependent adipogenesis reduction

in vitro with an IC_{50} value of 9.39µg/mL. The efficacy was associated with reduced levels of leptin, corticosteroids and serum lipid levels (Majeed *et al.*, 2022). Further, the stilbenoidspiceatannol, scirpusin A and scirpusin B were identified as the pharmacologically active molecules responsible for the anti-obesity properties in *Cyperus rotundus*.The tuber extract of *Cyperus rotundus* contains activators of β-adreno receptors that reduce obesity by stimulating thermogenesis of brown adipose tissue. The aqueous tuber extract of *Cyperus rotundus* reduces the body weight gain, organ weight, serum triglyceride level and the total cholesterol level in obese rats and a herbal supplement containing *Cyperus rotundus* rhizome extract was suggested for controlling obesity (Athesh *et al.,* 2014). *Scirpus* species has also relevance in obesity and obesity related diseases. *Scirpus yagara* extract was reported as anti-obesity agent on HFD-induced obesity (Wang *et al*., 2015).

Anti depressant activity

Depression is a psychiatric disorder which affects more than one-fifth of the global population (Wang *et al.*, 2019). It causes considerable burden on individuals and society with its high morbidity, recurrence and mortality (Feng *et al*., 2019). Currently, a number of antidepressants are used in the clinical treatment. However, disadvantages such as delayed onset time, inadequate response rate and side effects are reported for the current drugs (Clayton *et al.,* 2018). Medicinal plants have been reported to exert antidepressant effects through synaptic regulation of serotonin, noradrenaline and dopamine, regulating activity of hypothalamic-pituitary-adrenal axis, reinforcing anti-oxidant defence system, and decreasing inflammatory mediators. Medicinal plants and their active compounds can relieve depression through different pathways and hence are considered a new source to produce antidepressants (Zahra and Sana, 2017).

Zhou *et al.* (2016) investigated the antidepressant activity of *Cyperus rotundus* and its possible mechanism of action, and found to be significantly reducing depression. Xia *et al.* (2020) showed that *Cyperus rotundus* methanol extract has therapeutic potential against depression and may be attributed to SIRT3 stimulated neuroplasticity enhancement by NLRP3 inflammasome suppression. Hot water extract of *Cyperus eleusinoides* also showed antidepressant activity (Kokate and Varma, 1982).

Anti androgenic activity

An anti-androgen is a compound that has the biological effect of blocking or suppressing the action of male sex hormones such as testosterone within the body. Androgen dysregulation can give rise to a variety of clinical disorders, including polycystic ovarian syndrome, which affects 7% of the world's population. Though several androgen antagonists are available, in recent yearsthere has been an increasing demand for complementary and alternative therapies, especially using plant derived anti-androgen agents (Grant and Ramasamy 2012).

Flavonoids from *Cyperus rotundus* possesses estrogenic property, exerting an anti-androgenic effect on androgenic hair without disturbing the testosterone level (Tang *et al*., 2008). El-Kaream (2012) observed that the essential oils were effective against moderate hirsutism by inhibition of 5-α-reductase and 17-β-hydroxysteriod dehydrogenase without affecting the serum testosterone level. *Cyperus rotundus* essential oil is found to be effective for decreasing the growth of axillary hair.

Anti diarrheal activity

Diarrhoea is generally defined as the passage of abnormally liquid or unformed stools associated with increased frequency of defecation and abdominal pain (Guerrant *et al*., 2001). Despite reductions in morbidity and mortality worldwide, diarrhoea still accounts for more than 2 million deaths annually and is associated with impaired physical and cognitive development in resourcelimited countries. Medicinal plants are usually preferred to treat gastrointestinal disorders such constipation and diarrhoea, because they contain multiple constituents with less side effects (Gilani *et al.,* 2005).

Cyperus rotundus tubers have been traditionally used in several Ayurvedic formulations to treat diarrhea (Shamkumar *et al*., 2012). The aqueous extract of the plant is reported with antidiarrheal potential against castor oil induced diarrhea in mice and the pre-treatment of mice with aqueous extract decreases the purging frequency through an antisecretory mechanism. The petroleum ether and methanol extracts also showed antidiarrheal activity (Rahman *et al.,* 1986; Daswani *et al*., 2001). A moderate dose-dependent antidiarrheal activity was exhibited by the methanol extract of *Fimbristylis aphylla* (Islam *et al*., 2011).

The methanol extract of *Fimbristylis miliacea* also exerts strong antidiarrheal effect (Mukta *et al.*, 2020).

Anti convulsant activity

Epilepsy is a serious neural disease that affects around 50 million people all over the world. Although for the majority patients with epilepsy, seizures are well controlled by currently available antiepileptic drugs (AEDs), there are still around 30% of patients suffering from medically refractory epilepsy and approximately 30-40% of all epileptic patients are affected by numerous side effects and seizure resistance to the current AEDs. Therefore, many researchers try to develop novel approaches to treat epilepsy, especially through new antiepileptic constituents from herbal medicines.

Phytochemicals present in the rhizomes of *Cyperus rotundus* are known to have anticonvulsant properties (Sonwa and Konig, 2001; Shivakumar *et al.*, 2009). The methanolic extract of rhizomes of *Cyperus articulates* showed anticonvulsant activity in mice, by protecting maximal electroshock (MES) and pentylenetetrazol (PTZ)-induced seizures (Bum *et al*., 2001). The leaves extract of the plant also showed effect on pentylenetetrazol (PTZ) induced seizures in mice (Herrera-Calderon *et al*., 2017).

Anti genotoxic activity

Genotoxicity is the ability of different agents to produce damage to genetic material (Bhattacharya, 2011). The agents capable of causing genetic toxicity are described as genotoxic. Since the genotoxic agents are involved in the initiation and promotion of several human diseases, the significance of novel bioactive phytocompounds in counteracting these mutagenic and carcinogenic effects is now gaining credence.

Flavonoids and tannins in *Cyperus rotundus* extract synergistically exhibited antigenotoxic activity. The ethyl acetate extracts were found to be effective in reducing the production of thiobarbituric acid reactive substance (TBARS) and protecting against H_2O_2/UV induced DNA damage (Kilani *et al.*, 2008). Luteolin was found to be an active ingredient in reducing TBARS production and K562 cell proliferation. The antigenotoxic potential evaluated against nifuroxazide and AFB1-induced genotoxicity showed potential activity for ethyl acetate extract of *Cyperus rotundus* (Kilani *et al*., 2011).

Neuroprotective activity

Neuroprotection aims at preventing or slowing the loss of neurons. For neuroprotective assays, a number of neurotransmitters and signalling molecules have been identified as therapeutic targets. Conventional as well new molecules have been tried against these targets. Phytochemicals from medicinal plants play a vital role in maintaining the brain's chemical balance by influencing the function of receptors for the major inhibitory neurotransmitters (Halliwell, 1992).

Cyperus plant extracts have proven to have neuroprotective effect against damage due to reactive oxygen species (ROS). The deposition of β-amyloid in the hippocampus promotes oxidative stress, reactive oxygen formation, reduction of the antioxidant enzymes activity, and consequently, neuronal death. Previous studies have shown that the flavonoids can modulate the function of immune cells, exerting a direct effect against inflammation and oxidative stress (Dhillon *et al.,* 1993). Thus, the antioxidant activity showed by the flavonoids present in *Cyperus rotundus* extracts explains the increase in hippocampal neurogenesis of β-amyloid in rat models and consequently improves the memory (Shakerin *et al.,* 2020). The neuroprotective activity of *Cyperus rotundus* ethanol extract was assessed against sodium nitrate induced hypoxia injury and was found to be protecting rats against cognitive impairment, muscular co-ordination defects and locomotors defects. The oral administration of *Cyperus rotundus* ethanol extract prevented pyramidal cell loss in the CA1 region of hippocampus (Jebasingh *et al*., 2014). *Cyperus rotundus* extractattenuated peroxynitrite induced neurotoxicity and inhibited NO generation by downregulating i-NOS expression (Kumar *et al*., 2013).

Orientin, a flavonoid found in *Cyperus esculentus* decreased the oxidative stress, generating a neuroprotective effect against cerebral ischemia/reperfusion injury in Sprague-Dawley rats through the middle cerebral artery occlusion method (Jing *et al*., 2020). Treatment with TN extract restored Scop-induced learning and memory impairments. *Cyperus esculentus* extract lowered amyloid beta, β-secretase protein expression and acetylcholine esterase (AChE) activity in the hippocampus of rats, and also decreased malondialdehyde levels, restored antioxidant levels and reduced proinflammatory cytokines as well as the Bax/Bcl2 ratio (Saeed *et al*., 2022). *Fimbristylis ovata* extract significantly decreased the inflammatory cytokines under oxidative stress

induction. The plant reported to possess protective effects in SH-SY5Y, human neuroblastoma cell line, under neurotoxicity circumstance induced by AGEs (Sirirattanakul and Santiyanont, 2021).

Nootropic activity

According to the World Health Organization, approximately 450 million people suffer from a mental or behavioural disorder. Dementia, the age-related mental disorder, is a characteristic symptom of Alzheimer's Disease (AD). It is a progressive, neurodegenerative and cerebrovascular disease, destroying cells in the brain, causing problems with memory, unusual behaviour, difficulty in thinking, personality changes and ultimately leading to death. AD is characterized by the loss of neuronal cells and is primarily linked to neurofibrillary tangles and neuritic plaques. The cholinergic system in the brain plays an important role in learning and memory, which involves acetylcholine. Dementia is produced due to reduction of Ach in the brains of patients with AD. Medicinal plants are used for memory enhancement from ancient times onwards. In rodents and human beings, drugs like scopolamine impair learning and memory (Dinesh *et al*., 2004).

Cyperus rotundus has been traditionally used as a memory enhancer to treat memory loss and cognition, and experiments revealed that *Cyperus rotundus* significantly increased the memory (Sunil *et al*., 2011). Treatment with total oligomeric flavonoids fraction significantly reduced the neurological deficits and reversed the anxiogenic behavior in rats (Soman *et al*., 2013). However, the extracts and essential oils of *Cyperus rotundus* were inactive on scopolamine induced memory dysfunction in rats (Rabbani *et al*., 2014).

Anti endometriosis and anti dysmenorrhea activities

Pain associated with menstruation is called dysmenorrhea, and medicinal plants are used for the treatment of dysmenorrhea in various traditional medicinal systems across the globe. The rhizome of *Cyperus rotundus* showed significant antidysmenorrhea effect in mice model and the compounds spathulenol and β-caryophyllene oxide were found as the active compounds (Yoon *et al*., 2015).

Endometriosis is characterized by the presence and growth of endometrial tissue outside the uterus in the peritoneal cavity. It affects approximately 6-10% of women of reproductive age. *Cyperus rotundus* extract exerts anti-endometriotic activities by the

inhibition of cell adhesion and neurotrophin expression, through the negative regulation of the Akt and NF-kB pathways in endometriotic cells (Ahn *et al*., 2022).

Anti parasitic activity

Antiparasitic drugs are a group of medications used in the management and treatment of infections by parasites including protozoa, helminths and ectoparasites. Infections by parasites are often treated by plant products or secondary metabolites isolated from medicinal plants. Malaria, caused by the parasite *Plasmodium* sp., is a life-threatening disease and a leading cause of illness and death in many developing countries. Natural products isolated from plants have been a good source of lead compounds used to treat various infectious diseases, including malaria. Two examples of phenomenal lead compounds that have greatly contributed in reducing malaria deaths worldwide are quinine isolated from the Andes tree *Cinchona officinalis* and artemisinin isolated from the Chinese medicinal plant *Artemisia annua*. However, *Plasmodium* has shown in the last few decades increasing resistance to antimalarial drugs, highlighting the need to identify novel anti-malarial compounds from plant resources (Schwikkard *et al*., 2002).

Methanol extract and essential oil of *Cyperus rotundus* rhizome inhibited the survival of *P. falciparum* (Thebtaranonth *et al*., 1995). Members of the genus *Scleria* would be worth being evaluated for their antiplasmodial properties. Efange *et al.* (2009) isolated the antiplasmodial sesquiterpene endoperoxide okundoperoxide from *Scleria striatinux* and was found active *in vitro* againstthe amoeba *Naegleria fowleria* and also against *Schistosoma japonicum, S. mansoni* and *Clonorchis sinensis* (Hien and White, 1993). *Cyperus articulatus* extract showed *in vitro* antiplasmodial activity against two strains of *P. falciparum* (Assis *et al.,* 2020). *Cyperus brevifolius* ethanol extract of aerial parts abolished the motility of *Eudrilus eugeniae* (Pucblos *et al.,* 2017).

Insecticidal activity

The major Cyperaceae member *Cyperus rotundus* is also attributed with remarkable insecticidal and larvicidal activities. Studies revealed that the tuber extracts of *Cyperus rotundus* were effective for repellency of the entire mosquito vector even at low dose (Singh *et al*., 2009). *Cyperus rotundus* was more effective insecticidal than carbamate and

has almost the same efficacy as that of organophosphate against the tested ants (Solita *et al*., 2011). The ovicidal and larvicidal efficacy of essential oils of the tubers of *Cyperus rotundus* was studied on eggs and fourth instar larvae of *Aedes albopictus.* The eggs and larvae were exposed to serial concentration of the oils ranging from 5-150 ppm and observed for 24 h. Oils showed remarkable ovicidal and larvicidal activities indicated by EC_{50} value of <5 ppm and LC_{50} value of <20 ppm (Vivek *et al.,* 2008).

Toxicological studies

Toxicology testingis the process of determining the degree to which a substance of interest negatively impacts the normal biological functions of an organism, given certain exposure duration, route of exposure, and substance concentration. Pharmacological activity analyses of medicinal plant extracts are associated with toxicity evaluation and need to report the feasible dosage level of various plant extracts.

A review of the pharmacological activities reported for various Cyperaceae members revealed the diverse bioactivities, as claimed by traditional herbal information, and the toxicological assays revealed the safety for human use in medicinal and food sector (**Table 1**). Different extracts of *Cyperus rotundus* in various dosages revealed no toxic effect even at higher dosages up to 4000 mg/kg, with no signs or symptoms of toxicity and recommends the rhizomes and tubers of *Cyperus rotundus* as safe for human use (Thanabhorn *et al*., 2005). Roy *et al*. (2022) studied the acute and subchronic toxicity profile of the methanol extract of the leaves of *Fimbristylis miliacea* and suggests that the plant has no toxicity.

Table 1. Pharmacological activities of Cyperaceae members

Sl. No.	Pharmacological properties	Cyperaceae species	Reference
1.	Analgesic activity	*Cyperus eleusinoides*	Kokate and Varma, 1982
		Cyperus rotundus	Imam *et al*., 2014 Chen *et al.*, 2011
		Fimbristylis aestivalis	Talukder *et al*., 2022
2.	Anti androgenic activity	*Cyperus rotundus*	Tang *et al.*, 2008 El-Karеam 2012

3.	Anti arthritic	*Cyperus rotundus*	Biradar *et al*., 2010
		Cyperus esculentus	Biradar *et al*., 2010
		Cyperus eleusinoides	Kokate and Varma, 1982
4.	Anti bacterial activity	*Carex humilis*	Seo, 2015
		Cyperus conglomerates	Hisham *et al*., 2012
		Cyperus esculentus	Dimayuga *et al*., 1998
		Cyperus incompletes	Dini *et al*., 1992
		Cyperus scariosus	Lahariya, 1979
		Cyperus rotundus	Buckley *et al*., 2014 Peerzada *et al*., 2015 Khojaste *et al*., 2018 Al-Hazmi *et al*., 2018 Sharma and Singh, 2011
		Cyperus sphacelatus	Mfonku *et al*., 2021
		Cyperus kyllinga	Khamsan *et al.*, 2011
		Cyperus longus	Swamy *et al*., 2016
		Cyperus papyrus	Lawal *et al*., 2016
		Fimbristylis aphylla	Islam *et al*., 2011
		Rhynchospora corymbose	Pagning*et al*., 2016
		Scleria striatinux	Mbah *et al*., 2012 Nayim *et al.*, 2022
		Scirpus holoschoenus	Saliha *et al*., 2017
		Carex cruciata	Bogucka-Kocka *et al*., 2011
		Carex alopecuroides	Bogucka-Kocka *et al*., 2011
		Carex baccans	Bogucka-Kocka *et al*., 2011
5.	Anti cancer activity	*Cyperus tegetum*	Chatterjee *et al*., 2022
		Cyperus exaltatus	Kim *et al*., 2022

		Cyperus rotundus	Ahn *et al.*, 2015 Bisht *et al.*, 2011 Huang, 2020 Park *et al.*, 2014 Samra *et al.*, 2021 Simorangkir *et al*., 2019 Wang *et al.*, 2021
		Cyperus conglomerates	Al-Nuairi *et al*., 2020
		Carex folliculate	Sarrias *et al*., 2011
		Carex gynandra	Sarrias *et al*., 2011
		Fimbristylis aestivalis	Talukder *et al*., 2022
		Carex cruciata	Bogucka-Kocka *et al*., 2011
		Carex alopecuroides	Bogucka-Kocka *et al*., 2011
		Carex baccans	Bogucka-Kocka *et al*., 2011
6.	Anti convulsant activity	*Cyperus rotundus*	Sonwa and Konig, 2001 Shivakumar *et al*., 2009
		Cyperus articulatus	Herrera-Calderon *et al*., 2017
7.	Anti depressant activity	*Cyperus eleusinoides*	Kokate and Varma, 1982
		Cyperus rotundus	Zhou *et al*., 2016 Xia *et al*., 2020
8.	Anti diarrheal activity	*Cyperus scariosus*	Shamkumar *et al*., 2012 Rahman *et al*., 1986 Daswani *et al*., 2001
		Fimbristylis aphylla	Islam *et al*., 2011
		Fimbristylis miliaceae	Mukta *et al*., 2020
9.	Anti dysmenorrhea activity	*Cyperus rotundus*	Yoon *et al.*, 2015
10.	Anti genotoxic activity	*Cyperus rotundus*	Kilani *et al.*, 2008 Kilani *et al.*, 2011

11.	Anti hypoxia activity	*Cyperus rotundus*	Jebasingh *et al*., 2014
12.	Anti inflammatory activity	*Cyperus iria*	Vera *et al*., 2022
		Cyperus rotundus	Jin *et al.*, 2011 Mardiana *et al*., 2020 Huang *et al*., 2018 Rocha *et al.*, 2020 Khan *et al*., 2011 Tsoyi *et al*., 2011 Mardiana *et al*., 2020
		Cyperus conglomeratus	El-Shamy *et al*., 2020
		Carex cruciata	Bogucka-Kocka *et al*., 2011
		Carex alopecuroides	Bogucka-Kocka *et al*., 2011
		Carex baccans	Bogucka-Kocka *et al*., 2011
		Carex humilis	Lee *et al.*, 1998
		Scirpus yagara	Li *et al*., 2014
13.	Anti obesity activity	*Cyperus rotundus*	Sureshkumar and Mishra, 2005 Parvez *et al*., 2019 Yoon *et al*., 2015 Majeed *et al*., 2022 Athesh *et al*., 2014
		Cyperus alternifolius	Awaad *et al*., 2012
		Scirpus yagara	Wang *et al*., 2015
14.	Anti oxidant activity	*Cyperus alternifolius*	Ahmed, 2012
		Cyperus articulates	Rakotonirina *et al*., 2001 Kavaz *et al.*, 2019
		Cyperus esculentus	Cook *et al*., 1998 Onuoha *et al*., 2017 Nwosu *et al*., 2022
		Cyperus rotundus	Kilani *et al*., 2008 Jihan *et al*., 2021
		Cyperus conglomeratus	Al-Rowaily *et al.*, 2019

		Cyperus capitatus	Al-Rowaily *et al.*, 2019
		Cyperus tegetum	Chatterjee *et al.*, 2019
		Cyperus compressus	Datta *et al.*, 2018
		Cyperus odoratus	Alif *et al*., 2018
		Scirpus holoschoneus	Saliha *et al*., 2017
		Carex stramentitia	Shimamura *et al*., 2007
		Carex alopecuroides	Shimamura *et al*., 2007
		Fimbristylis miliacea	Ramli *et al*., 2022
		Fimbristylis dichotoma	Ramli *et al*., 2022
		Scirpus articulates	Bhardwaj *et al*., 2014
		Scirpus articulates	Bhardwaj *et al*., 2014
15.	Anti parasitic activity	*Cyperus brevifolius*	Pucblo*et al.*, 2017
		Cyperus rotundus	Thebtaranonth *et al*., 1995
		Scleria striatinux	Hien and White, 1993
16.	Anti platelet activity	*Cyperus rotundus*	Seo *et al*., 2011
17.	Anti pyretic activity	*Cyperus rotundus*	Pal *et al*., 2009
		Fimbristylis miliacea	Roy *et al*., 2019
18.	Anti ulcer activity	*Cyperus rotundus*	Rahman *et al*.,1986 Daswani *et al*., 2001
		Cyperus alternifolius	Farrag *et al.,* 2019
		Cyperusconglomeratus	El Shamy *et al*., 2020
19.	Anti uropathogenic activity	*Cyperus rotundus*	Sharma *et al.*, 2014
20.	Anti viral activity	*Cyperus niveus*	Kaij *et al*., 1992
		Cyperus pangorei	Bhakuni *et al*., 1988
		Cyperus rotundus	Soltan and Zaki, 2009 Parvez *et al.*, 2019 Xu *et al*., 2020 Samra *et al.*, 2020 Vincent *et al.*,2020 Birendra Kumar *et al*., 2021 Khuntia *et al*., 2021
21.	Hepatoprotective activity	*Cyperus rotundus*	Sureshkumar and Mishra, 2005 Parvez *et al.,* 2019 Yoon *et al*., 2015 Athesh *et al*., 2014

		Cyperus alternifolius	Awaad, 2012
		Carex cruciata	Bogucka-Kocka *et al*., 2011
		Carex alopecuroides	Bogucka-Kocka *et al*., 2011
		Carex baccans	Bogucka-Kocka *et al*., 2011
22.	Neuroprotective activity	*Cyperus rotundus*	Jebasingh *et al.*, 2014 Dhillon *et al.*, 1993 Shakerin *et al*., 2020
		Cyperus esculentus	Jing *et al*., 2020
		Fimbristylis ovata	Sirirattanakul and Santiyanont, 2021
23.	Nootropic activity	*Cyperus rotundus*	Sunil *et al.*, 2011 Rabbani *et al*., 2014 Soman *et al*., 2013
24.	Wound healing activity	*Cyperus articulatus*	Mongelli *et al.*, 1995
		Cyperus rotundus	Puratchikody *et al*., 2006 Imam *et al*., 2014

Pharmacologically active phytochemicals reported from Cyperaceae members

Cyperaceae species are reported to contain different class of compounds such as aurones, chromones, coumarins, iridoids, flavonoids, stilbenoids, lignans, benzofurans, phenolic acids, phenyl propanoids, phenolic derivatives, sesquiterpene alkaloids, diterpenoids, triterpenoids, steroids, organic acids, aliphatic ketones, aliphatic acids, amides and other nitrogenous constituents. Various phytopharmacological assays have led to the identification of potential biological activities to the isolated compounds from the plant group.

Phenolic compounds

Among the diversity of phytochemicals reported from Cyperaceae members, phenolic compounds such as aurones, chromones, coumarins, iridoids, flavonoids, stilbenoids, lignans, benzofurans, phenolic acids and phenyl propanoids are attributed with various biological activities.

Stilbenoids

Stilbenoids are phenolic compounds consisting of two differently substituted aromatic rings, which is linked by an ethylene bridge. The aromatic rings differ in the number and position of functional groups, including hydroxy, methoxy, prenyl, geranyl or farnesyl moieties. Stilbenoids can also be classified as monomers or oligomers, and are isolated as aglycones or glycosides. Stilbenoids are largely studied in the last decades because of their bioactivities such as anti-inflammatory, neuroprotective, anticancer, antimicrobial and antidiabetic effects (Akinwumi *et al.,* 2018**).** These are important in chemotaxonomy as well and play a key role in plant defense mechanism. The most studied stilbenoid is resveratrol, which has been extensively investigated for its numerous potential health benefits including anti-oxidant, antimicrobial, anticancer, anti-inflammatory, antidiabetic, cardioprotective, anthelmintic, vasorelaxant activity and anti-aging effects. Recently, resveratrol has been identified as promising drug candidates against COVID-19 **(**Wahedi *et al*., 2021). The compound was proven to be a phytoestrogen as well (Baur and Sinclair; 2006).

More than 65 stilbenoids were isolated from 28 Cyperaceae species, while 14 stilbenoids were reported from *Cyperus rotundus* alone. Besides resveratrol, other monomeric (piceatannol and combretastatin A) and oligomeric (α-viniferin, hopeaphenol A, miyabenol C and kobophenol B) stilbenes with promising biological activities have also been isolated from Cyperaceae in recent years (**Figure 2)**.

α-Viniferin, a stilbene trimer isolated from *Carex gynandra* and *Carex folliculata* showed antiproliferative activity on HCT-116 cells with IC_{50} 6.6 µM (Gonzalez *et al*., 2011). α-Viniferin isolated from *Carex humilis* exhibited a dose dependent inhibitory activity (Lee, 1998). Among the various compounds isolated from Cyperaceae, trans-scirpusin B, a resveratrol oligomer was found to possess the most potent DPPH radical scavenging activity (SC_{50} = 2.8 µM) (Kawabata *et al.,* 1991). Cyperusphenol B, a benzylidene stilbene isolated from *Cyperus rotundus* rhizome was the most effective in scavenging free radicals in DPPH assay. Resveratrol and its derivatives, piceatannol, scirpusins A and B, isolated from *Scirpus californicus*, showed xanthine oxidase inhibitory activity (IC_{50} values 3.9, 3.6 and 6.0 µM, respectively) (Kawabata *et al.,* 1991; Schmeda *et al*., 1996; González *et al*., 2011). Piceatannol showed potent anti-inflammatory and antioxidant activity due to the

ability to form semiquinone radical. Majeed *et al.* (2022) investigated the antiobesity agents in *Cyperus rotundus* rhizomes and reported piceatannol, scirpusin A and scirpusin B as the pharmacologically active molecules

Carexanes, the marker compounds in *Carex* genus are stilbenoids with a rare tetracyclic structure, originated from prenylated stilbenes by cyclization, and were able to enhance the antioxidant response of HspB transfected human gastric epithelial (AGS) cells. Among the various caraxanes, carexane I proved to be the most active (Abrosca *et al*., 2005).

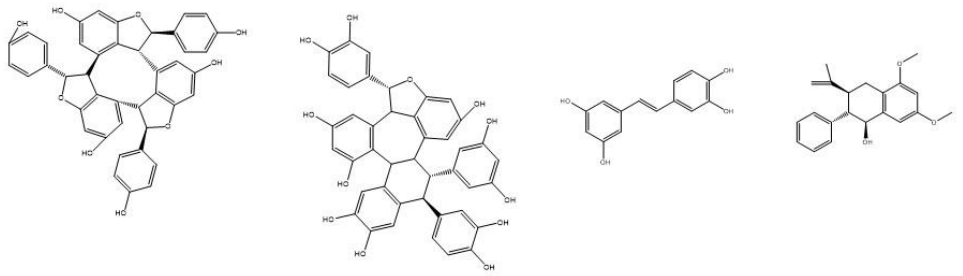

Figure 2. Major stilbenes reported from Cyperaceae members. α-Viniferin, cyperusphenol B, piceatannol and carexane I

Benzoquinones

Quinones are ubiquitous in nature, which occur predominantly in flowering plants. Benzoquinones such as 1,2-benzoquinones and 1,4-benzoquinones in plants are involved in important biological functions such as bioenergetic transport, oxidative phosphorelation and electron transport process.

Benzoquinones are important class of phytochemicals in Cyperaceae with promising pharmacological activities. Cyperaquinone, hydroxycyperaquinone, dihydrocyperaquinone, scabequinone and tetrahydrocyperaquinone are the major benzoquinones in Cyperaceae. Benzoquinones are important targets to develop new drugs that are more selective to cancer cells (Vera *et al.*, 2019). Anticancer studies showed that hydroxycyperaquinone is a novel sub-micromolar inhibitor of 20S catalytic core of the 20S proteasome, causing cell death *via*IRE1α-independent/PERK-dependent pathways. The new benzoquinone alopecuquinone isolated from the ethanol extract of the inflorescences of *Cyperus alopecuroids* by Nasser *et al.* (2002) showed moderate estrogenic activity using a strain

of *Saccharomyces cerevisiae* (**Figure 3)**. It has also been reported that the compoundhas medicinal effects such as pectoral emollient, analgesic and anti-helminthic properties.

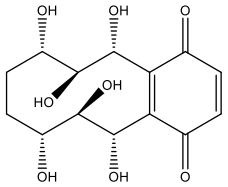

Figure 3. Thebenzoquinone alopecuquinone reported from *Cyperus alopecuroids*

Polyphenols

The polyphenols, ferulic acid, p-hydroxybenzaldehyde, p-coumaric acid, sinapinic acid, chlorogenic acid, luteolin and gallic acid reported from *Cyperus rotundus* exhibit potent antioxidant activity (Pelegrin *et al*., 2022) (**Figure 4)**.

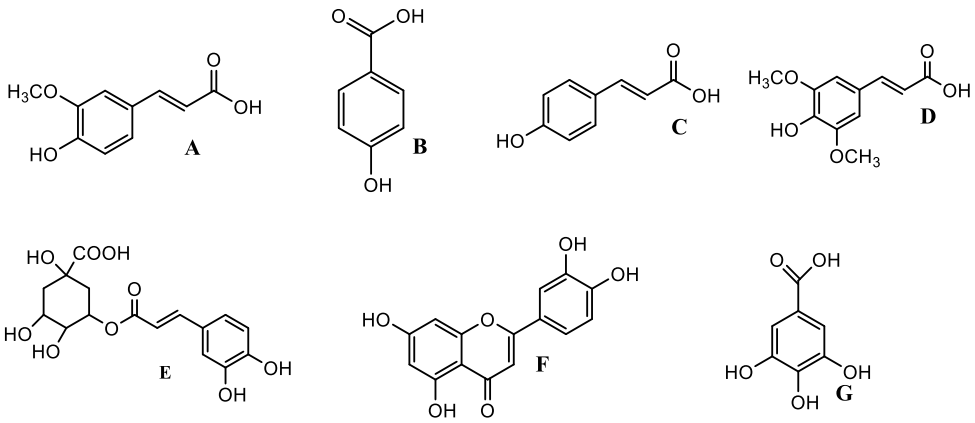

Figure 4. Major polyphenols reported from *Cyperus rotundus* **A**. Ferulic acid, **B**. p-Hydroxybenzaldehyde, **C**. p-Coumaric acid **D**. Sinapinic acid, **E.** Chlorogenic acid, **F.** Luteolin, and **G.** Gallic acid

Sesquiterpenoids

Sesquiterpenoids, made up of three isoprene units, are a class of enormously diverse natural products derived from farnesyl pyrophosphate and exist in a wide variety of forms including acyclic, monocyclic, bicyclic and tricyclic frameworks. These are important compounds in the essential oils of plants and are potent pharmaceutical agents due to the

versatile biological activities. Sesquiterpenoids are the major subclass of natural products reported from the essential oils of various Cyperaceae members. Diverse structural skeletons such as patchoulane, rotundane, eudesmane, guaiane, cadinane, caryophyllane, clovane and copaene have been reported from various Cyperaceae members (Yang and Shi, 2012). In addition, sesquiterpene endoperoxides, nor-sequiterpenoids and seco-sesquiterpenoids are also reported from the plant group. Major sesquiterpenoids with potential biological activities reported from various Cyperaceae are elaborated below.

Cyperotundone

Cyperotundone is a sesquiterpene ketone with patchoulene type frame work found in many essential oils especially in *Cyperus rotundus* and *Cyperus articulates* (**Figure 5).** Pharmacological analysis revealed that the compound could be used as an anti-inflammatory and anti-viral agent, and also exhibited inhibitory activity on tumour necrosis factor-α induced activation of the NF-κB pathway, with half-maximal inhibitory concentration values ranging from 34.5 to 73.7 μmol/L (Wang *et al*.; 2021). The compound and its derivatives showed moderate anti-hepatitis B virus activity (Xu *et al*., 2015).

Rotundene

Rotundene is a characteristic sesquiterpenoid reported in *Cyperus rotundus* with azulene type frame work (**Figure 5)**. The anti-inflammatory and analgesic properties of the compound have been studied in detail. *In vitro* cytotoxicity assay with MTT indicated that rotundene is very effective against L1210 leukaemia cells line. This result correlates with significantly increased apoptotic DNA fragmentation. The oxidative effects of the compound evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH), xanthine/xanthine oxidase assays revealed the antioxidant potential of the compound (Kilani *et al*., 2008). The potential peripheral and central analgesic properties of the compound were also studied extensively (Rabelo *et al.*, 2014).

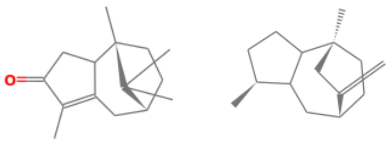

Figure 5. Cyperotundone and Rotundene

Mustakone

Mustakone is a tricyclic sesquiterpenoid and the name is derived from 'mustuka', the common name for *Cyperus rotundus* in India (**Figure 6)**. Swain *et al*. (2022) studied the inhibitory activity of *Cyperus articulates* components against *Staphylococus aureus* and proved the antibacterial activity of mustakone. Further the antifungal activity of the compound was examined against *Candida* species and showed positive response (Vaijayanthimala *et al*., 2000). The compound isolated from *Cyperus articulatus*was active against the sensitive strains of *Plasmodium falciparum* (Rukunga *et al*., 2008).

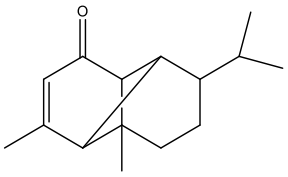

Figure 6. Mustakone

Nootkatone

Nootkatone, another potential sesquiterpenoid widely distributed in Cyperaceae members, showed insecticidal activity against *Plutella xylostella*, and also antibacterial activity and α-glucosidase inhibitory activity (Guo *et al*., 2020; Alkhaibari *et al*., 2021) (**Figure 7)**. It exhibits strong anti-inflammatory effects in LPS-stimulated RAW 264.7 cells (Park *et al*., 2021). Among the various compounds detected from *Cyperus rotundus* ethanolic extract, (+)-nootkatone was found to have the most potent inhibitory effect on collagen, thrombin and AA induced platelet aggregation, proving itsantiplatelet activity (Seo *et al*., 2011).

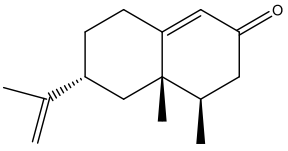

Figure 7. Nootkatone

α-Cyperone

α-Cyperone, a characteristic sesquiterpenoid isolated from *Cyperus rotundus* and other Cyperaceae members, exhibit strong anti-inflammatory effects in LPS-stimulated RAW 264.7 cells (**Figure 8)**. The compound also exerted antidepressant-like actions in a mouse depression model, and the antidepressant activity of the compound was attributed to

SIRT3/ROS pathway mediated NLRP3 inflammasome deactivation, which led to the enhancement of neuroplasticity. The findings revealed the antidepressant property of α-cyperone, and suggest targeting SIRT3/ROS signaling in depression treatment (Xia *et al*., 2020). α-Cyperone is associated with the down-regulation of COX-2, IL-6, Nck-2, Cdc42 and Rac1, resulting in reduction of inflammation, which would be highly beneficial for treatment of inflammatory diseases such as Alzheimer's disease (Zhang *et al*., 2022).α-Cyperone is a potential molecule for reduction of inflammation by destabilization of microtubule fibres in brain (Azimi *et al*., 2016). The compound had a pronounced influence on the tubulin structure, decreased polymerization rate and reduced concentration of polymerized tubulin *in vitro.*

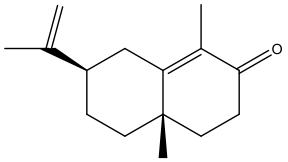

Figure 8. α-Cyperone

α-Corymbolol

The eudesmane type sesquiterpenoid α-corymbololisolated from *Cyperus rotundus* inhibited the HBV DNA replication with IC_{50} values ranging from 10.1 to 75.9 μM, and the results suggested the potential utility of the compound as an anti-HBV target **(Figure 9)** (Xu *et al*; 2015)**.**

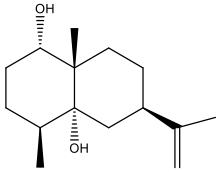

Figure 9. α-Corymbolol

Cyperene

Cyperene is one of the major constituents of various Cyperaceae species (**Figure 10)**. Molecular docking studies on selected phytochemicals in *Cyperus rotundus* with 5-α reductase enzyme revealed the sesquiterpene cyperene showing good interactions and can be used as a potential herbal medicine for Hirsutism disorders (Shirkoli *et al*.; 2018).

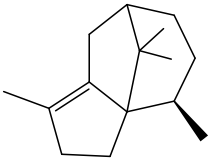

Figure 10. Cyperene

Ceramide

The amide, ceramide (2`-[2-hydroxypentacosanoylamino]-1`,3`,4`-nonadecanetriol) isolated from *Cyperus rotundus* showed promising anticancer activity and displayed inhibitory activity against HepG2 with IC_{50} values 6.81 to 8.07 µM, and PC3 with IC_{50} of 11.92 to 14.48 µM (Samra *et al*., 2021) (**Figure 11)**.

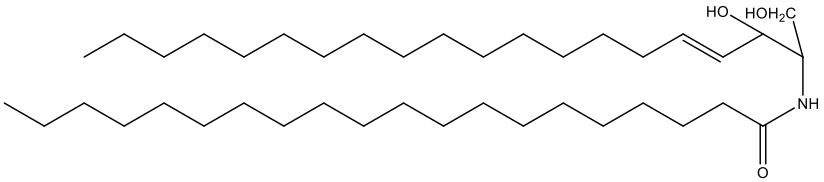

Figure 11. Ceramide

Translational research in Cyperaceae members

The pharmacological screening and phytochemical standardisation of various Cyperaceae plants, based on the traditional medicinal applications have led to the development of a wide array of products and patents out of the plant group. Various extracts as well as active compounds thereof are patented for the biological activities from different Cyperaceae members, especially on *Cyperus rotundus*. The major patents are on menopausal disorders, dental hygiene, antiseptic, cosmetic, anti-inflammatory, anti-obesity, neurodegenerative disease, stress release and antiulcer sectors.

Cyperus rotundus finds its mention in ancient ayurvedic literature as a drug capable of 'de-fatting' adipose or muscular tissues (Trivedi and Mann, 1972). The plant has been mentioned in *Charak Samhita* as lekhaniya category, indicating its anti-obesity property. Crude extract of *Cyperus rotundus* was reported to have an anti-obesity activity (Zbinden *et al*., 2007; Oh *et al*., 2016). It was demonstrated that the administration of 45 mg/kg/day of *Cyperus rotundus* tubers hexane extract for 60 days in Zucker rats induced a significant

reduction in weight gain without affecting food consumption or inducing toxicity. *In vitro*, 250 µg/mL of this extract was able to stimulate lipolysis in 3T3-F442 adipocytes suggesting that this medicinal plant contains activators of β-adrenoreceptors (Bernard *et al*., 2007). The anti-adipogenic mechanism was evaluated in a diet-induced mice model of obesity and adipocytes *in vitro*. *Cyperus rotundus* hexane extract showed a dose-dependent adipogenesis reduction *in vitro* with an IC_{50} value of 9.3µg/mL. The active constituents have been identified as the stilbene derivatives piceatannol, scirpusin A and scirpusin B, and aherbal product has been developed as a health adjuvant for managing hypercholesterolemia and obesity in humans with the rhizomes of *Cyperus rotundus* as the major component (Majeed *et al*., 2022).

Another interesting application of *Cyperus rotundus* is in dental care products. The plant had been reported to be used since the pre-historic times, as evidenced from the dental plaque analysis of prehistoric skeletons. The usage of *Cyperus rotundus* explains the unexpectedly low frequency of caries among the Meroitic populations of Al Khiday, as *Cyperus rotundus* has the ability to inhibit *Streptococcus mutans* that causes dental caries (Buckley *et al*., 2014). Various pharmacological assays have further confirmed the anticariogenic properties of *Cyperus rotundus* (Yu *et al*., 2007). Based on the traditional applications as well as the pharmacological evidences, various products and patents were developed with *Cyperus rotundus* for the treatment and prevention of periodontitis and tooth decay (Khojaste *et al*., 2018).

Conclusion

An update of the progress in pharmacological properties of Cyperaceae plants reveals that though the plant group is widely distributed with extensive traditional applications in medicinal sector, and a plethora of interesting structures have been identified from the plant group, intensive explorations are needed on pharmacological activities to attain a greater clarity of the mechanism of action. Modern approaches like structure-activity relations correlating the plethora of structural features with pharmacological activities using modern computational tools will lead to a better perception of the underlying molecular mechanisms. In addition, validated clinical trials are also needed to explore as per the norms to accept the traditional claims of the Cyperaceae plants.

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