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Pharmaceutical & Biomedical Research

Review Article :

A Review on Cyperus rotundus: Ancient Weed to Modern Elixir of Life Phytochemistry and Therapeutic Uses of Cyperus rotundus (Mustaka)

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ABSTRACT

Background: Since time immemorial, humans have identified several herbs to treat various ailments. With the advancement of science and state-of-the-art technologies, different herbal extracts and chemical constituents of herbs were identified as therapeutic targets. Cyperus rotundus, also called mustaka, is one of the most ancient herbs widely distributed in tropical and subtropical regions across the globe. The tuberous and aerial parts of the herb were identified to possess various pharmacological properties.

Objectives: This review focuses on the various phytocompounds of mustaka and how these compounds exert pharmacological effects and their mode of action. The molecular and cellular effects of mustaka were also discussed based on the preclinical and clinical reports available using an array of in vitro, in vivo, and ex vivo methodologies.

Methods: The information from Google Scholar, Science direct, PUBMED, were reviewed with a special focus on the mode of action of C. rotundus from the data on animal and preclinical experiments to treat various diseases.

Conclusion: Based on the literature available on C. rotundus in Google Scholar, Science Direct, and PubMed, the pharmacological properties of mustaka were reviewed with a particular focus on its neuropharmacological activities. The mode of action of C. rotundus and its bioactive metabolites at the molecular biology level were demonstrated based on animal and preclinical experiments to cure various ailments. These diverse effects prove C. rotundus as a valuable traditional medicine for treating various disorders.

Introduction

Herbal extracts and their chemical components are extensively studied to identify their various pharmacological effects. These studies advanced the effective utilization of herbal extracts as a traditional and alternative medicine to cure various ailments due to their fewer or no side effects. The commercialization and popularization of herbal extracts have led to their wide utilization as an ayurvedic medicine to treat various disorders. However, there is still a surge in the identification and commercialization of herbal medicines with no genotoxic and cytotoxic effects for treating various diseases. *Cyperus rotundus* is a weed distributed across tropical and subtropical regions, including India, Africa, Tunisia, and other countries. *C. rotundus* is one of the oldest medicinal herbs used from the age of Charaka to cure various diseases (Figure 1) [1]. In ancient times, *C. rotundus* powder was used as a flavoring agent on cooked meat, and the starch of the tuber was extracted to prepare noodles [2]. Recent studies also incorporated *C. rotundus* in minced beef meat to improve the quality, storability, and safety [3].

Several studies previously reported that *C. rotundus* possess anti-bacterial, anti-fungal, and mosquito-repellent activities [4, 5]. *C. rotundus* possesses various pharmacological properties, such as anti-inflammatory, anti-obesity, anti-diabetic, and neuroprotective effects [4, 6-8]. Our group also reported that *C. rotundus* possess strong free radical scavenging, anti-oxidant, and lipid peroxidation properties using an array of in vitro anti-oxidant and free radical scavenging activities. We also studied the in vivo anxiolytic and cognitive effects of *C. rotundus* in animal models of anxiety and hypobaric hypoxia in mice and rats, respectively [9, 10]. The oxide-nitrosative and anti-apoptotic effects of *C. rotundus* against hydrogen peroxide (H_2O_2), an oxidative stress insult and 3-morpholinosydnonimine (SIN-1), a nitrosative stress insult induced cytotoxicity were reported from our lab using SH-SY5Y cells, a widely used human cell line model to study neuronal stress/neuroprotective effects [11, 12]. Besides, we reviewed the ex-vivo anti-oxidant and antihemolytic effects of *C. rotundus* using H_2O_2 induced oxidative stress in White Blood Cell (WBC) and 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced hemolysis in WBC [9, 13].

However, little is known on the mode of action of *C. rotundus* and its chemical constituents on various ailments at the molecular level. Hence in the present review article, we discuss the diverse pharmacological effects of *C. rotundus* and its phytochemicals in treating various diseases based on in vitro, in vivo, and ex vivo studies using animal, cell culture, and clinical studies. Here we discuss the interaction and mode of action of *C. rotundus* in regulating these ailments at the molecular level.

Cyperus rotundus taxonomical classification and cultivation

Cyperus rotundus L. (family: Cyperaceae), commonly known as musta, mustaka, nutgrass, java grass, purple nutsedge, red nutsedge [14], is native to India, Africa, southern and central Europe, and southern Asia [15]. It is widely distributed in tropical and subtropical regions worldwide [16]. *C. rotundus* is listed by Theophrastus [17] among other perfume plants of which "the most excellent and most fragrant come from Asia and sunny regions" (Historia Plantarum, IX 7.3). The genus name *Cyperus* is derived from the ancient Greek name Cypeiros, and the species name *rotundus* is from the Latin word round, which denotes the plant tuber [18]. It is a perennial sedge with umbel inflorescence, and fibrous roots reproduce widely through rhizomes and tubers. It is a widespread species under unfavorable conditions and is today considered the most troublesome weed in agriculture due to its competitive nature for ground nutrients with herbicide tolerance and high adaptability, which cause large yield losses [19]. However, it possesses various ethnomedicinal uses and therapeutic properties comprising essential oil and other phytochemical constituents. The most common targets of mustaka and its constituent include transcription factors, enzymes, growth factors, cytokines, kinases, proliferative factors, inflammatory mediators, receptors, and proteins involved in cell survival, apoptosis and metastasis (Figure 2).

Phytochemical Analysis of C. rotundus

Phytochemical analysis of herbal extracts has been investigated by various analytical techniques using sophisticated instruments, such as gas chromatography-mass spectrometry (GC-MS), high performance liquid chromatography (HPLC), and liquid chromatography-mass spectrometry (LC-MS) [20, 21]. The major phytochemicals of *C. rotundus* include essential oils, flavonoids, terpenoids, sesquiterpenes, sitosterol, cyperene, cyperol, nootkatone, and valencene [7, 22]. Sesquiterpene alkaloids, such as rotundines A, B, and C, were isolated from *C. rotundus* [23]. Chen et al. [24] analyzed the active constituents of *C. rotundus* by GC–MS, which shows the presence of α-cyperone. The phenolics and flavonoids are other groups of secondary metabolites which possess anti-oxidants and free radical scavenging activities

[25]. *C. rotundus* possesses phenolic compounds, such as 3-hydroxy-4-methoxy-benzoic acid, galloylquinic acid, ferulic acid, and flavonoid compounds, such as quercetin, luteolin, afzelechin, catechin [26]. Qualitative tandem liquid chromatography quadrupole time of flight mass spectrometry (LC-Q-TOF/MS) analysis of *C. rotundus* hydroethanolic fraction showed the presence of scaberin, auresidin, cyperol, 4,6,3,4-tetramethoxyaurone, luteolin 5-methyl ether, epoxycaryophyllane-5alpha,15-diol, 4-hydroxybenzoic acid, alpha cyperone, 4-7,-dimethyl-1-tetralone, p-coumaric acid, *Cyperus*ol D, sulfuretin, juvenile hormone III, rotundine B, isokubosone, rotundine, beta rotunol, *Cyperus*ol B2, *Cyperus*ol A1, 6,3,4,-trihydroxy-4-methoxy-5-methylaurone, dolabella-3,7,18-triene, whereas Total Oligomeric Flavonoid fraction (TOF) fraction showed the presence of 4,6,3,4-tetramethoxyaurone, rotundine B, eudesma-2,4(15)-11-triene, *Cyperus*ol D, γ-calacorene, 4,7-dimethyl-1-tetralone, β-rotunol, isocorymbolone [13, 27].

Phytochemicals of essential oils of *Cyperus rotundus* are as follows: monoterpene hydrocarbons; camphene, limonene, p-cymene, sabinene, α-pinene, β-pinene, oxygenated monoterpenes derivatives; 1,8-cineole, terpinen-4-ol, α-terpineol, carvacrol, borneol, myrtenol, terpinolene, thymol, oxygenated sesquiterpenes derivatives; α-cadinol, (2E, 6E)-farnesol, α-cyperone, T-muurolol, elemol, mustakone, caryophyllene oxide, cubenol, T-cadinol, eugenol, monoterpene aldehydes; myrtenal, monoterpene ketones; carvone, dihydrocarvone, sesquiterpene hydrocarbon; α-copaene, aromadendrene, β-elemene, valencene, (E,E) α-farnesene, α-humulene, β-caryophyllene, γ-elemene, sesquiterpene ketones; nootkatone, sesquiterpene aldehyde; cinnamaldehyde, flavonoids; luteolin 3′-methyl ether, luteolin 7,3′-dimethyl ether, luteolin 5,3′-dimethyl ether, luteolin 7-glucuronide, luteolin 4′-glucoside, orientin, quercetin, quercetin 3-rutinoside, kaempferol, triterpenoid; n-tritriacontan-16-one, n-pentadecanyl-9-octadecenoate, n-tetradecanyl-n-octadec-9, 12-dienoate, khellin, visnagin, ammiol, khellol-β-D-glucopyranoside, phenylpropanoids; isoaragoside, chionoside A, pungenin, salidroside, helioside C, alkaloids; rotundine A, rotundine B, rotundine C, phenolic acids; gallic acid, chlorogenic acid, caffeic acid, p-coumaric acid, loganic acid, ferulic acid, ellagic acid, iridoides, benzodihydrofurans, and other compounds; *rotundus*ide A, *rotundus*ide B, *rotundus*ide C, *rotundus*ide, 10-O-p-hydroxybenzoylthevirido-side, 10-O-vnilloyltheviridoside, 6″-O-(trans-p-coumaroyl)-procumbide, 6-O-p-coumaroylgenipin gentiobioside, 1-[2,3-dihydro-6-hydroxy 4,7-dimethoxy-2S-(prop-1-en-2yl)benzofuran-5-yl]ethanone, 1α-methoxy-3ß-hydroxy-4α-(3′,4′dihydroxyphenyl)-1,2,3,4 tetrahydronaphthalene, 1α,3β-dihydroxy-4α-(3′,4′-dihydroxyphenyl) -1,2,3,4-tetrahydronaphthalene, n-butyl-β-D-fructopyranoside

ethyl-α-D-glucopyranoside, trans-(2-chlorovinyl) dimethylethoxysilane, 5-hydroxymethyl furfural, vanillin lactoside, 2-propenoic acid, 3-(4-hydroxy-3-methoxy phenyl)-methyl ester, 9, 12, 15-octadeca trienoic acid, 2, 3-bis [(trimethyl)oxy] propyl ester, methyl 3,4-dihydroxy benzoate, ipolamiide, 6b-hydroxyipolamiide, and rutin. The major phytochemicals of *C. rotundus* are presented in Table 1 with their classifications, molecular formula, and structures.

Neuro-pharmacological Effects of C. rotundus

The nervous system is highly vulnerable to the stress induced by external and internal stimuli that leads to neurodegeneration and cognitive decline. Various herbal extracts were determined as safe due to fewer side effects. They were evaluated by various preclinical methods and used across the globe from time immemorial because of their valuable properties [12, 28]. Understanding the mode of actions of different known exogenous and endogenous chemical agents or environmental agents that damage the nervous system or the herbal compounds or extracts that inhibit the neuronal damage is an interesting area of research. This line of research has strong potential in identifying novel neuro-pharmacological drugs to treat an array of neurodegenerative ailments. Various studies demonstrated the neuropharmacological effects of *C. rotundus* as presented in Table 2.
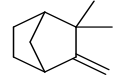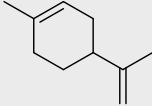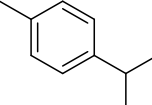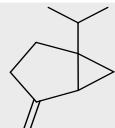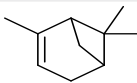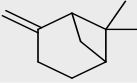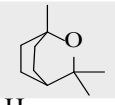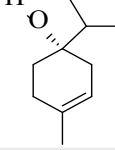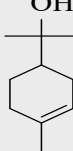
Anti-alzheimer activity of C. rotundus
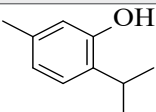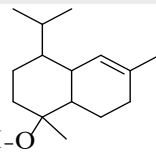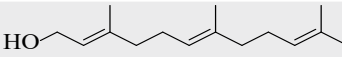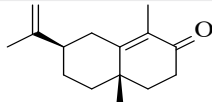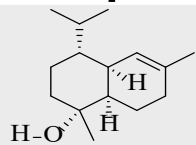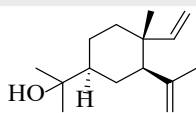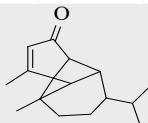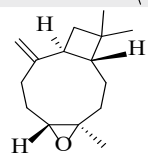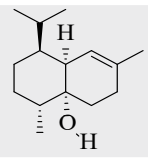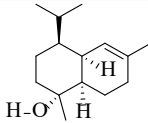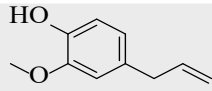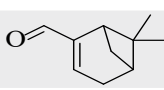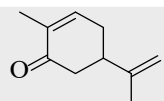
Alzheimer Disease (AD) is an irreversible, progressive disorder that leads to cognitive impairment and neurodegeneration. Amyloid plaques, microtubule fibers, and neurofibrillary tangles are observed in the brains of patients with AD. Oxidative stress is known to play a key role in the pathogenesis of AD [29]. The hydroalcohol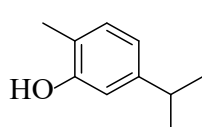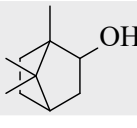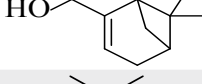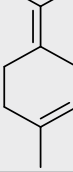ic fraction of *C. rotundus* improved learning impairment, following the amyloid β peptide (Aβ) treatment-induced memory impairment in rats [30]. α-Cyperone, one of the major compounds of *C. rotundus*, binds and interacts with tubulin and destabilizes microtubule polymerization, and further reduces inflammation associated with AD [31].
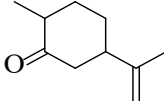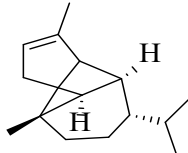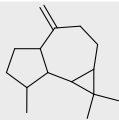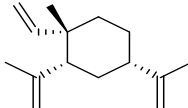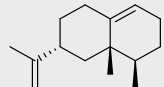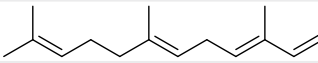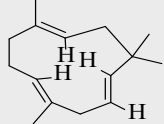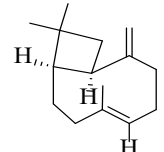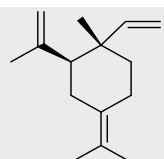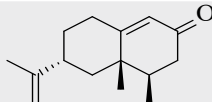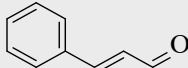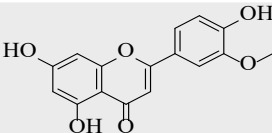
Anti-Parkinson Effects of C. rotundus

Parkinson disease is a progressive neurological disease in which degeneration of the dopaminergic neurons in the brain plays a key role in neurodegeneration. Lee et al. [32] reported the neuroprotective activity of water extract

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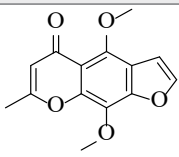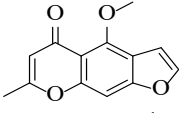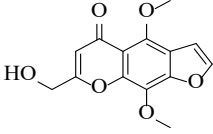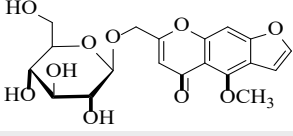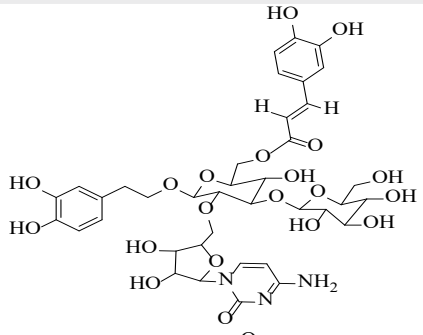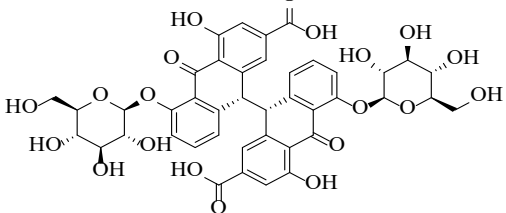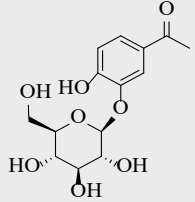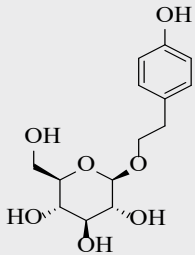
Table 1. Phytochemicals of cyperus rotundus according to their classification, molecular formula, and chemical structures
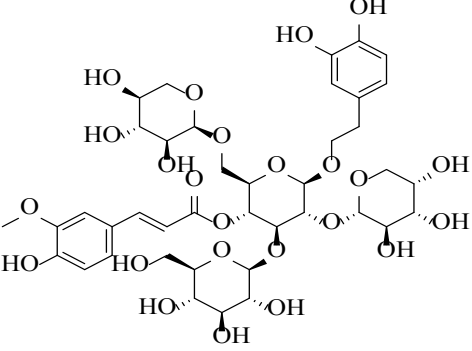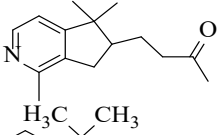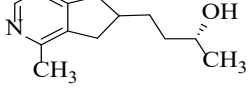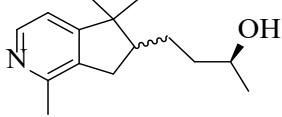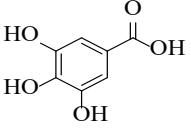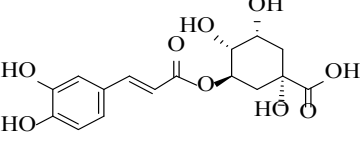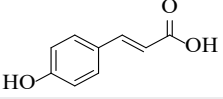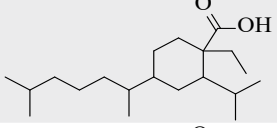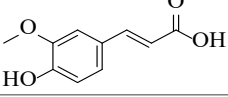
Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Camphene	C10H16		[89]
Limonene	C10H16		[90]
p-Cymene	C10H14		[89]
Sabinene	C10H16		[91, 92]
α-Pinene	C10H16		[93, 94]
β-Pinene	C10H16		[93]
Oxygenated monoterpenes derivatives			
1,8-Cineole	C10H18O		[95, 96]
Terpinen-4-ol	C10H18O		[97]
α-Terpineol	C10H18O		[98]
Carvacrol	C10H14O		[99]
Borneol	C10H18O		[100]
Myrtenol	C10H16O		[101]
Terpinolene	C10H16		[102]
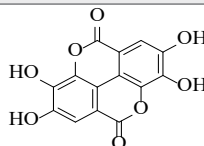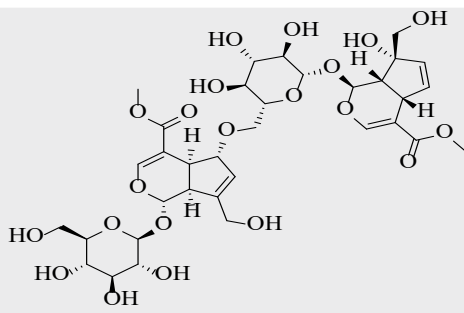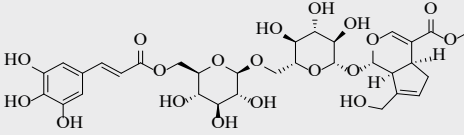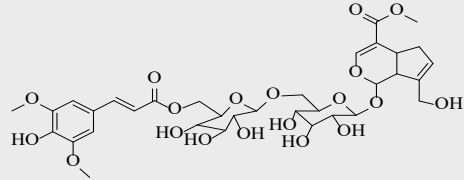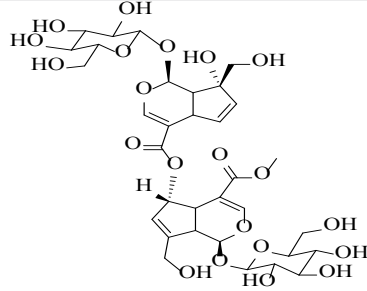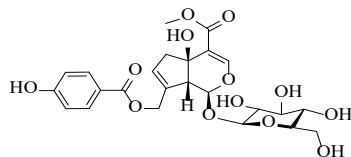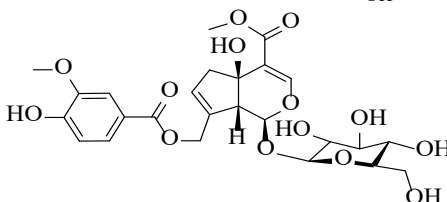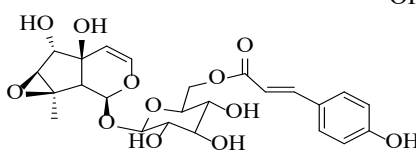
Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Thymol	C10H14O		[103, 104]
Oxygenated sesquiterpenes derivatives			
α-Cadinol	C15H26O		[105]
(2E,6E)-Farnesol	C15H26O		[106]
α-Cyperone	C15H22O		[107]
T-Muurolol	C15H26O		[108]
Elemol	C15H26O		[109]
Mustakone	C16H22O		[110]
Caryophyllene oxide	C15H24O		[111]
Cubenol	C15H26O		[112]
T-Cadinol	C15H26O		[113]
Eugenol	C10H12O2		[114]
Monoterpene aldehydes			
Myrtenal	C10H14O		[115]
Monoterpene ketones			
Carvone	C10H14O		[116, 117]
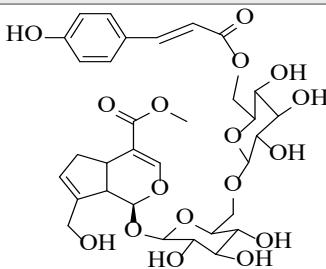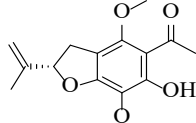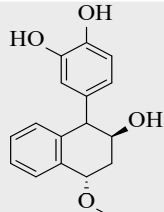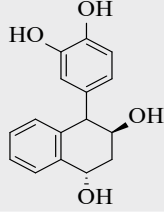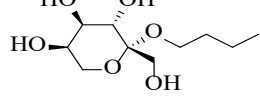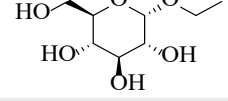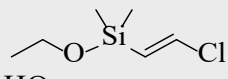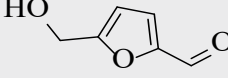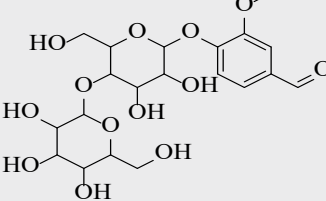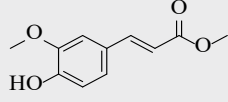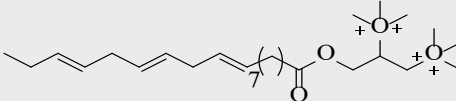
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Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Dihydrocarvone	C10H16O		[118]
Sesquiterpene hydrocarbon			
α-Copaene	C16H24		[119]
Aromadendrene	C15H24		[120]
β-Elemene	C15H24		[121]
Valencene	C15H24		[7]
(E,E)-α-Farnesene	C15H24		[122]
α-Humulene	C15H24		[123, 124]
β-Caryophyllene	C15H24		[125, 126]
γ-Elemene	C15H24		[127]
Sesquiterpene ketones			
Nootkatone	C15H22O		[7, 128, 129]
Sesquiterpene aldehyde			
Cinnamaldehyde	C9H8O		[130, 131]
Flavonoids			
Luteolin 3'-methyl ether	C16H12O6		[132]
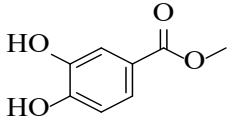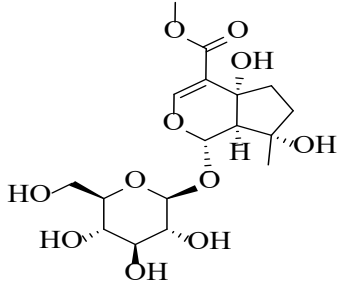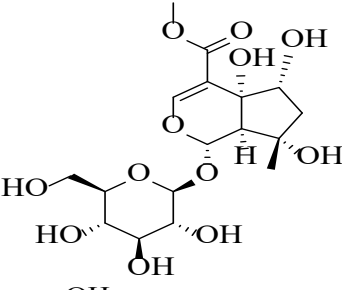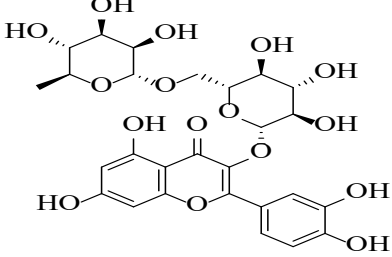
Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Luteolin 7, 3'-dimethyl ether	C17H14O6		
Luteolin 5, 3'-dimethyl ether	C17H14O6		[133]
Luteolin 7-glucuronide	C21H18O12		
Luteolin 4'-glucoside	C21H20O11		
Orientin	C21H20O11		[134]
Quercetin	C15H10O7		
Quercetin 3-rutinoside	C27H30O16		[132]
Kaempferol	C15H10O6		
Triterpenoid			
n-Tritriacontan-16-one	C33H66O		
n-Pentadecanyl-9-octadec-enoate	C33H63O2-		[135]
n-Tetradecanyl-n-octadec-9, 12-dienoate	C32H59O2-		

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Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Khellin	C14H12O5		
Visnagin	C13H10O4		[133]
Ammiol	C14H12O6		
Khellol-β-D-glucopyranoside	C19H20O10		
Phenylpropanoids			
Isoaragoside	C38H47N3O20		[136]
Chionoside A	C42H38O20		
Pungenin	C14H18O8		[137]
Salidroside	C14H20O7		

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Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Helioside C	C40H54O24		[136]
Alkaloids			
Rotundine A	C15H21NO		
Rotundine B	C15H23NO		[23]
Rotundine C	C15H23NO		
Phenolic acids			
Gallic acid	C7H6O5		
Chlorogenic acid	C16H18O9		[138]
Caffeic acid	C9H8O4		
p-Coumaric acid	C9H8O3		
Loganic acid	C20H38O2		[136]
Ferulic acid	C10H10O4		[138, 139]

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Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Ellagic acid	C14H6O8		[140]
Iridoides, benzodihydrofurans, and miscellaneous			
Rotunduside A	C34H46O21		[136]
Rotunduside B	C32H40O19		
Rotunduside C	C34H44O19		[137]
Rotunduside	C33H44O21		
10-O-p-Hydroxybenzoylthe-virido-side	C24H28O13		[141]
10-O-Vnilloyltheviridoside	C25H30O14		
6''-O-(trans-p-Coumaroyl)-procumbide	C24H28O12		

Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
6-O-p-Coumaroylgenipin gentiobioside	C32H40O17		[136]
1-[2,3-Dihydro-6-hydroxy-4,7-dimethoxy-2S-(prop-1-en-2yl) benzofuran-5-yl]ethanone	C15H18O5		[142]
1α-Methoxy-3ß-hydroxy-4α-(3',4'dihydroxyphenyl)-1,2,3,4 tetrahydronaphthalene	C17H18O4		[143]
1α,3β-Dihydroxy-4α-(3',4'-dihydroxyphenyl) -1,2,3,4-tet-rahydronaphthalene	C16H16O4		
n-Butyl-β-D-fructopyranoside	C10H20O6		[140]
Ethyl-α-D-glucopyranoside	C8H16O6		
trans-(2-Chlorovinyl) dimeth-ylethoxysilane	C6H13ClOSi		
5-Hydroxymethyl furfural	C6H6O3		
Vanillin lactoside	C20H28O13		[144]
2-Propenoic acid, 3-(4-hy-droxy-3-methoxy phenyl)-methyl ester	C11H12O4		
9, 12, 15-Octadeca trienoic acid, 2, 3-bis [(trimethyl)oxy] propyl ester	C27H52O44+		

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Phytochemicals of C. rotundus	Molecular Formula	Structure	References
Monoterpene hydrocarbons			
Methyl 3,4-dihydroxy benzo-ate	C8H8O4		
Ipolamiide	C17H26O11		
6b-Hydroxyipolamiide	C17H26O12		[145]
Rutin	C27H30O16		

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of *Cyperus* in an in vitro model of PC12 cells. The authors reported that 50 and 100 µg/mL doses of the extract restored 50% of cell death challenged by 6-hydroxydopamine, which exerts Parkinson-like effects by mediating oxidative damage. The extract efficiently reduced Reactive Oxygen Species (ROS), Nitric Oxide (NO) formation, and dissipated Mitochondrial Membrane Potential (MMP). Further, the extract downregulated caspase-3 expression, a biomarker of apoptosis, and effectively rescued the dopaminergic neuronal damage analyzed by tyrosine hydroxylase immunostaining, which is a biomarker of neurodegeneration suggesting the potential neuroprotective mechanism of the *Cyperus* extract.

Anti-anxiety activity of C. rotundus

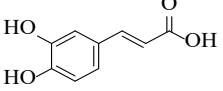Anxiety is a condition that every human experiences during their lifetime, but if it persists for a long duration, it develops as a mental illness that affects the psychological well-being of an individual [33, 34]. Several drugs, including benzodiazepines that non-selectively target GABAA receptors, are used as anxiolytics to treat anxiety [35]. However, several herbal remedies are also demonstrated as an anxiolytic [9, 34]. Our group demonstrated that hydroalcoholic extract of *C. rotundus* exhibits anxiolytic effects in a mouse model evaluated by an array of behavioral tests [27]. In a previous study, Sunil et al. [8] also demonstrated that the TOF fraction of *C. rotundus* reversed the anxiogenic behavior in rats and decreased the neurological deficits against cerebral ischemia-reperfusion injury.

Anti-depression property of C. rotundus

Depression is a psychological disease characterized by a sense of persistent sadness and or loss of interest. Natural mood enhancements and herbal supplements ease mild depression and are recommended as therapy. Wei et al. [36] evaluated the anti-depressive activity of

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Table 2. Therapeutic, medicinal, and industrial applications of cyperus rotundus

Biological activity/ Application	Experimental Design	Results	References
In vitro anti-oxidant	Free radical scavenging assays like 2,2-diphenyl-1-picrylhydrazyl (DPPH), ABTS, superoxide, hydroxyl, nitric oxide, xanthine oxide, hydrogen per-oxide, and metal chelating, reducing power, lipid peroxidation activities	The ethanolic, methanolic, ethyl acetate, water, total oligomeric flavonoid, and oil fractions and active compounds such as stilbene dimers, cassigarol E, scirpusin A and B, cyperusphenol B, noot-katone, aristolone, solavetivone, ethyl-alpha-D-glucopyranoside (2), adenosine, (-)-(E)-caffeoylmalic acid, isovitexin, luteolin 7-O-β-D-glucuronopyranoside-6''-methyl ester, luteolin 4'-O-β-D-glucuronopyranoside, luteolin 7-O-β-D-glucuronopyranoside, uridine and of C. rotundus leaves, flowers and rhizomes exhibited potent free radical scavenging activities.	[9, 26, 59, 62-64, 86, 146-150]
Anti-bacterial	Bacillus pumilis, S. pyogenes, Escherichia coli, Shigella flexneri, Staphylococcus aureus, Klebsiella pneumonia, Enterobacter aerogenes, Salmonella paratyphi, Pseudomo-nas aeruginosa, Proteus vulgaris, Salmonella typhimurium, Salmonella typhimurium, Salmonella enteritidis, Enterococcus faecalis	Rhizome / Hexane, Ethanol, Acetone, Aqueous, Methanol, Fruit/oil, Aerial parts, Lyophilized infusion, Total oligomeric flavonoids, Ethyl acetate	[57-61]
Anti-fungal	Candida albicans	Ethanol extract	[151]
Anti-viral	Herpes Simplex-1 Virus (HSV)	Tuber	[152]
Anti-malarial	African malaria vectors (Anopheles gambiae and Anopheles arabiensis)	Cedrol, a sesquiterpene alcohol	[153]
Anti-plasmodial	Plasmodium falciparum	Ethyl acetate	[154]
Ovicidal and larvicidal	Aedes albopictus	Tubers-essential oil	[155]
Mosquito repellent	Anopheles culicifacies	Hexane extract of the tuber	[4]
Insecticidal	Blattella germanica	Steam distillate constituents of C. rotundus (L.) rhizome	[156]
Anti-obese	The anti-obese property was verified using Obese Zucker rats and 3T3-F442 adipocytes	C. rotundus hexane fraction for 60 days exhibited a significant reduc-tion in weight gain and stimulated lipolysis and thermogenesis by binding to β-adrenoreceptors in 3T3-F442 adipocytes	[6]
Hypolipidemic	Mechanism of amentoflavone on inhibition of uterine tumors.	Biflavone constituents of C. rotundus	[72]
α-Amylase and α-glycosidase inhibi-tory property	α-Glucosidase and α-amylase inhibi-tory activities were evaluated by in vitro enzyme inhibition assays which contribute to the antihyperglycemic activity.	Acarbose, tricin, isorhamnetin, oreintin, vitexin, myric-etin 3-O-β–D-galactopyranoside, isovitexin, luteolin 7-O-β–D-glucuronopyranoside, luteolin 4'-O-β–D-glucuronopyranoside, myric-etin 3-O-β-D-galactopyranoside, protocatechuic acid, ellagic acid, chlorogenic acid, orientin, epiorientin, isorhamnetin, luteolin 7-O-β–D-glucuronopyranoside, luteolin 4'-O-β–D-glucuronopyranoside, (_)-(E)-caffeoylmalic acid, caffeic acid, p-coumaric acid, tricin, salicylic acid vitexin, isovitexin, methanolic extract/ 3,4',5,6,7,8-hexahydroxy-flavane, cassigarol E, scirpusin A and B	[140, 150]
Protein glycation, pro-tein carbonylation, protein oxidation, and protein nitration inhibition	Fructose, AAPH, 3-morpholinosyd-nonimine (SIN-1) mediated damage of bovine serum albumin (BSA) was verified.	Ethanolic extract of C. rotundus aerial part and rhizome inhibits fructose-induced protein glycation, protein carbonyl content, AAPH/SIN-1 mediated protein oxidation, protein nitration, and 3-nitroty-rosine.	[54, 86]
Anti-diabetic	The anti-diabetic activity was checked in alloxan-induced hyperglycemic rats	C. rotundus hydroalcoholic extract at 500 mg/kg oral administration for seven days reduced blood glucose levels.	[146]
Wound healing	Wound healing activity	Ethanol fraction of rhizome	[157]
Anti-mutagenic	Salmonella typhimurium assay, Antimutagenic activity against Afla-toxin and sodium azide in TA100 and TA1535 assay system	Total Oligomeric Flavonoid (TOF) and ethyl acetate and methanol extracts from aerial parts of C. rotundus	[62]
Anti-diarrheal	The anti-diarrheal activity was checked against castor oil-induced diarrhea in mice.	Methanol and petroleum ether fractions of C. rotundus exhibited anti-diarrheal activity	[80]
Anti-platelet	C. rotundus 70% extract and its active compounds were checked for anti-platelet activity by rat platelet aggregations in vitro and ex vivo, and on mice, tail bleeding assays.	Among the active compounds, nootkatone exhibited the most po-tent anti-platelet effects, followed by 4-Cymene, β-pinene, 1,8-cin-eole, limonene, valencene, caryophyllene oxide, and coumarin.	[128]

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Biological activity/ Application	Experimental Design	Results	References
Anti-allergic	Sesquiterpenes and monoterpenes of C. rotundus were evaluated for anti-allergic activity in rat basophilic leukemia (RBL)-1 cells.	Sesquiterpenes inhibited 5-lipoxygenase production in RBL)-1 cells and hexosaminidase release in antigen-stimulated RBL-2H3 cells. Valencene and nootkatone also inhibited the delayed-type hyper-sensitivity in mice.	[76]
Anti-inflammatory	MTT assay, real-time PCR assay, ELISA, western blot analysis, siRNA transfections of heme oxygenase-1(HO-1) and Nrf2 with murine microglial cell line BV-2, neuroblastoma cell line SH-SY5Y cells, and hippocampal cell line HT22 cells, InnoZyme TACE activity assay, in vitro anti-inflammatory activity using THP-1 monocytic cells and in vivo anti-inflammatory activity were confirmed by carrageenan-induced rat paw edema as a model.	α-Cyperone, ingredients of C. rotundus oil decreased the production of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) in LPS-induced BV-2 cells, anti-inflammatory activity in activated macrophage, α-cyperone inhibit PMA-induced endothelial cell protein C receptor (EPCR) shedding through PKC pathway, lupeol showed potent IL-1 β activity inhibition in THP-1 monocytic cells and also displayed significant in vivo anti-inflammatory activity, isocyperol, a sesquiterpene from rhizomes suppress septic shock through negative regulation of pro-inflammatory factors.	[66, 158-160]
Analgesic	Treatment of antipyretic and analgesic activities, acetic acid-induced mice stretching model, acetic acid-induced writhing assay	The crude extract of C. rotundus exhibited the dose-dependent spas-molytic effect in rabbit jejunum by inhibiting the spontaneous and K+ (80 mM)-induced contractions, essential oil from fresh rhizome shows good analgesic effect. TOF-enriched extract	[24, 134, 161, 162]
Anti-proliferative	Thiazolyl blue tetrazolium bro-mide (MTT) assay	Terpene derivatives had anti-proliferative activity against the HCT116 cell line.	[163]
Anti-genotoxic	Chromosome aberrations assay	Aqueous, ethyl acetate, methanol, and TOF-enriched extracts exhibit no genotoxic activity	[161]
Anti-carcinogenic	(MTT) assay, migration assay in different cancer cell lines, electro-physiological recordings, western blot analysis, terminal deoxynucleotidyl transferase dUTP nick end labeling assay, caspases activity assay	Methanolic extract of C. rotundus rhizome (MRCr) showed signifi-cant anticancer activity, the effect of amentoflavone on inhibition of uterine tumors, valencene (1) from the rhizomes inhibits skin photoaging-related ion channels and UV-induced melanogenesis in B16F10 melanoma cells, 6-acetoxy cyperene (ethanol extract) from rhizome induce apoptosis in ovarian and endometrial cancer cells	[72-74]
Acetylcholinesterase (AChE) inhibition property	2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing anti-oxidant power (FRAP) assays.	Ethanol extract of C. rotundus inhibits AChE.	[49]
Anti-convulsant	Tonic seizures induced by maximal electroshock (MES) and pentylenetet-razole (PTZ).	Ethanol extract significantly reduced hindlimb extension and convul-sion duration in albino rats.	[14]
Neuroprotective	Morris water maze test (determina-tion of spatial memory), western blot analysis, Nissl staining	Enhanced memory increased neuronal density, with activated pERK1/2 were observed in the hippocampus of an extract of C. rotundus and Zingiber officinale (CP1) treated rats. Cyperus etha-nolic extract (CRE) constituents of scirpusin A and scirpusin B have therapeutic use against neurodegenerative diseases. EECR prevents pyramidal cell loss in the CA1 region of the hippocampus.	[11, 48, 49, 54, 164]
Sedative, anti-anxiety, anti-depressant	Sesquiterpenes of C. rotundus were examined by radiobinding assay using rat cerebrocortical brain slices. Anti-depressant effect of a polyherbal formulation Yueju-Wan extract com-posed of C. rotundus was checked for its anti-depressant activity in mice model by locomotor activity, tail suspension, and forced swim tests. The anxiolytic activity of 70% ethanol fraction of C. rotundus was checked by behavioral tests, such as open field, light-dark box, elevated plus maze, and Vogel conflict tests.	Ethyl extract fraction isolated sesquiterpene, isocurcumenol was found to be benzodiazepine receptor agonist explaining the sedative effects of C. rotundus. Supplementation of mice with Yueju-Wan extract showed anti-depressant effects. Oral administration of mice with C. rotundus at 200 mg/kg showed anxiolytic effects.	[9, 36, 46]
Flooding tolerance	C. rotundus grown in upland and low land ecosystems were compared in terms of growth habits, carbo-hydrate reserves and metabolism, and activities of enzymes involved in alcoholic fermentation, such as alcohol dehydrogenase and pyruvate decarboxylase.	The study demonstrates that the enzyme activities and soluble sugars were regulated, favoring the high growth of the weed C. rotundus in lowland ecosystems than uplands in a hypoxic environ-ment which poses a major threat to rice fields.	[165]

Biological activity/ Application	Experimental Design	Results	References
Phytoremediation property	Bioaccumulation coefficient as a measure of phytoremediation, total petroleum hydrocarbon (TPH)	Petroleum hydrocarbons contaminated sites, phytoremediation of chromium by aquatic and terrestrial weeds	[166-168]
Food application	Supercritical fluid extraction with carbon dioxide	The optimum yield of C. rotundus oil (1.82%) was found under the following conditions: temperature, 37.6°C; pressure, 294.4 bar; extraction time, 119.8 min; and CO2 flow rate 20.9 L/h.	[169]

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the Chinese poly-herbal formulation Yueju-Wan (which possesses *Cyperus rotundus*) by behavioral analysis in a mice model. The extract efficiently reduced the immobility time analyzed by tail suspension and forced swimming tests but did not significantly affect locomotor activity. These outcomes may result from the active components of the herbal formulation, among which α–cyperone is the one suggesting the possible anti-depressive activity of *Cyperus* extract.

The neurological properties of the ethanolic extract of *Cyperus* were evaluated by Pal et al. [37] in a mice model. The authors calculated the LD50 of ethanolic extract as 240 mg/kg, IP. The sleeping time was potentiated maximally with 80 mg/kg of the extract and hypnotics pentobarbitone, diazepam, and meprobamate and exhibited analgesic activity and further potentiated the analgesic activity induced by morphine and pethidine. Additionally, the extract efficiently increased the survival time, decreased the mortality rate against strychnine and leptazol-induced convulsions, and also reduced behav-

ioral reflexes suggesting the potential anti-depressive action of the *Cyperus* extract.

Anti-epileptic/anti-convulsant activity of C. rotundus

Epilepsy is a group of seizures characterized by abnormal recurrent and spontaneous electrical discharge of cerebral neurons, and its control requires continuous anti-convulsant medication. Khalili et al. [38] described the neuroprotective property of hydroalcoholic extract of *Cyperus* in mice model by pentylenetetrazole (PTZ-induced kindling), which mimics epilepsy-induced seizures in rats and mice. The hydroalcoholic extract of *C. rotundus* efficiently ameliorated the PTZ-induced seizure formation and reduced epilepsy-associated neuro-oxidative stress and restored the anti-oxidant status of the brain in an in vivo model of epilepsy [38, 39].

Sedative activity of C. rotundus

Sedatives or tranquilizers act on the nervous system and induce sleep by reducing irritability or excitement. The sedative and analgesic effect of *C. rotundus* with its essential oil and crude extract was evaluated at a dose of 300 and 500 mg/kg bodyweight by tail-flick method on mice [24, 40]. Dilipkumar et al. [41] showed that *C. rotundus* extract has an analgesic effect and significantly potentiated the sleeping time of mice induced by standard hypnotics (diazepam). The sedation action might be due to enhancing brain serotonin and GABAergic transmission [42].

Anti-nociceptive activity of C. rotundus

The body contains nociceptive receptors that recognize neuropathic or nociceptive pain usually caused by an injury, physical pressure, or inflammation of some part of the body. Hydro-methanolic extract of *C. rotundus* exhibits anti-nociceptive activity and inhibits thermal- and chemical-induced pain in mice. A study also demonstrated that *C. rotundus* did not cause any mortality,

Figure 1. Cyperus rotundus

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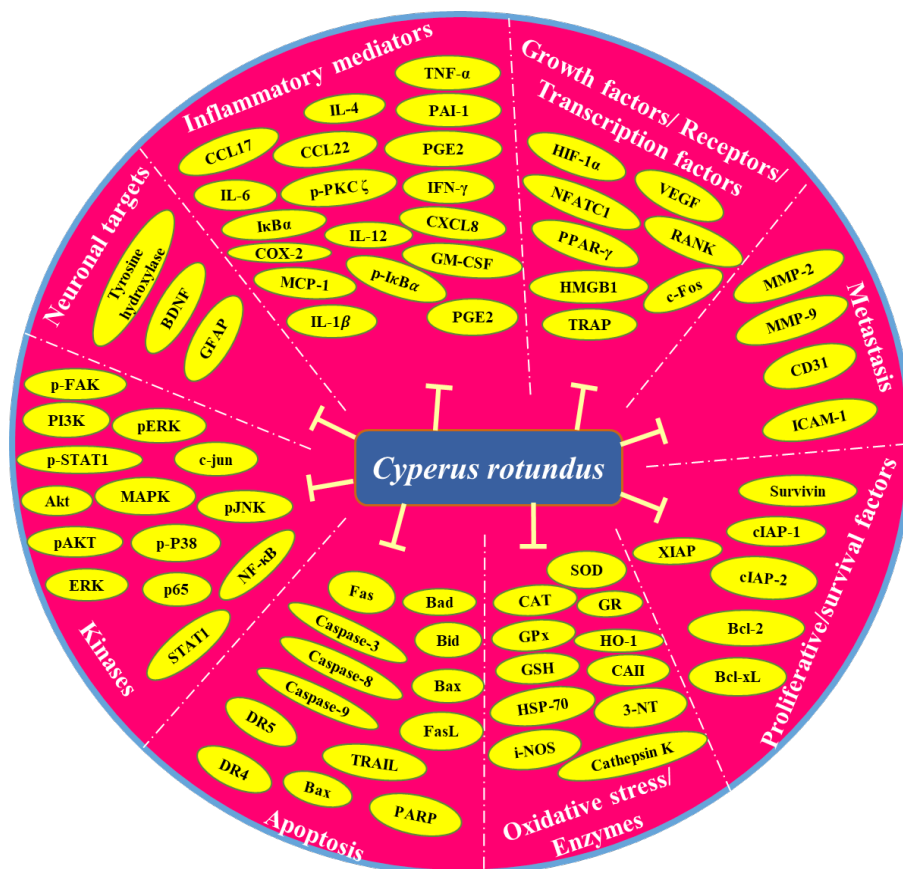
Figure 2. Molecular Targets of Cyperus rotundus and Its Bioactive Compounds

behavioral changes, or allergic reactions and is safe up to 3000 mg/kg body weight in mice [43].

Nootropic effects of C. rotundus

The medications that exert neurological relief/neuroprotection and aid in the psychological well-being of individuals are considered nootropics [44, 45]. In an earlier study, Ha et al. [46] demonstrated the γ-aminobutyric acid (GABAA)-benzodiazepine (BZR) receptor activity of *Cyperus* extract. Activation of BZR, a key component of the GABA receptor complex, enhances the actions of GABA, an inhibitory neurotransmitter, on the Cl- conductance of the neuronal membrane. The authors demonstrated the rat cerebrocortical BZR receptor agonistic activity of methanol, ethyl acetate fractions, and isocurcemenol from ethyl acetate fraction by receptor binding assay.

Lee et al. [47] reported the neuroprotective activity of Ondamtanggamibang (ODG), a traditional Korean herbal remedy that encompasses 15% of *Cyperus* extract by using in vitro model of PC12 cells. About 600 μg/mL of ODG restored cell viability with hydrogen peroxide and 6-hydroxydopamine (6-OHDA) challenge, respec-

tively, reducing ROS formation. The HO-1 gene expression is up-regulated with an increasing concentration of ODG. In contrast, zinc protoporphyrin IX (ZnPP-IX), an inhibitor of heme oxygenase-1(HO-1), the treatment showed poor cell viability against H_2O_2 challenge with ODG treatment. Also, cycloheximide and actinomycin-D inhibited ODG induced HO-1 expression, suggesting the possible protective role of ODG in oxidative stress via HO-1 expression.

In an elegant study, Sunil et al. [8] described the neuroprotective activity of Total Oligomeric Flavonoids (TOF) of *Cyperus* by in vivo model of cerebral-ischemia reperfusion injury (IR). In this study, 200 mg/kg TOF extract alleviated the neurological dysfunction and sensorimotor performance compared with IR rats. The extract also decreased the brain glutamate, glutamine synthetase activity and increased the Na+K+ATPase activity, thus reducing the excitotoxicity, a key event in neuronal dysfunction. The extract showed potential anti-anxiety activity evaluated by rats' behavioral functions and protected the degeneration of neurons as analyzed by histopathological sectioning of the brain. Furthermore, TOF treatment restored the anti-oxidant status of the IR brain,

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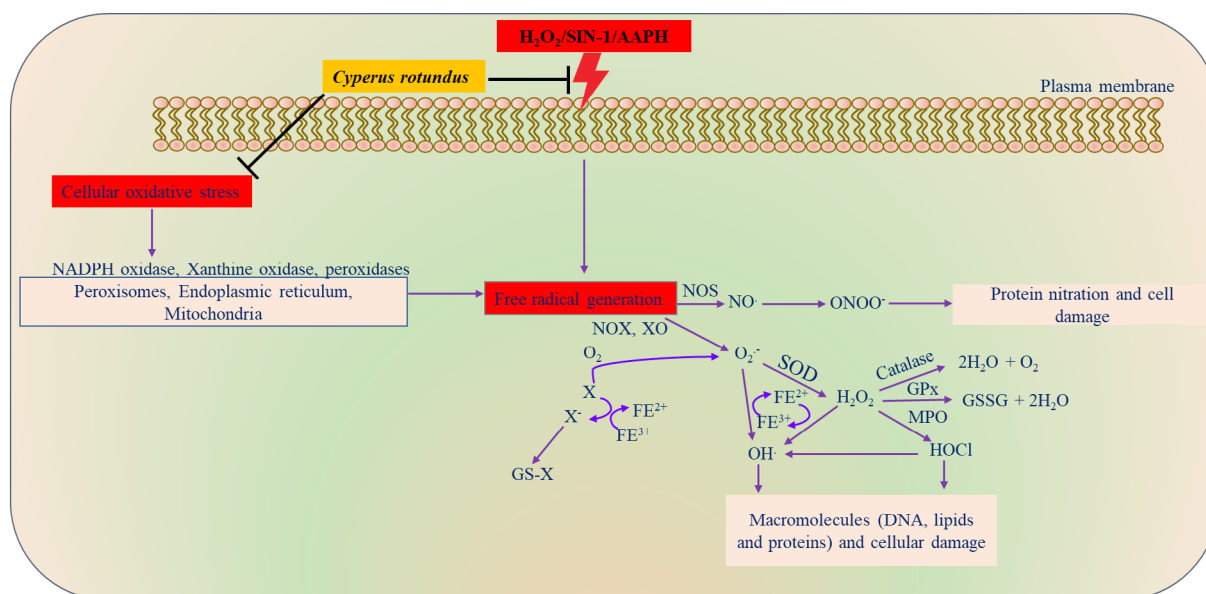
Figure 3. Cyperus rotundus Inhibiting Oxide-nitrosative Stress in Nervous System

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Extrinsic and intrinsic free radicals mediate oxide-nitrosative stress, such as NADPH oxidase, xanthine oxidase, myeloperoxidase, peroxidases due to peroxisomes, endoplasmic reticulum. Also, mitochondria stress induces macromolecules, such as DNA, lipid, and protein damage and mitochondrial ROS to mediate neurodegeneration.

explaining the potential role of flavonoids in neuroprotection.

Memory impairment modulating activity of C. rotundus

Neurodegeneration as a consequence of neurological diseases such as Alzheimer, Parkinson, or due to ischemia, hypobaric hypoxia impairs the cognitive ability of individuals by damaging CA1 and CA3 regions of the hippocampus. These areas play a crucial role in memory and recognition ability. Various preclinical mice/rat models determined that *C. rotundus* administration inhibits neurodegeneration and memory impairment and prevents pyramidal cell loss in CA1 and CA3 regions of the hippocampus. Ethanolic extract of *C. rotundus* prevents ischemia, hypobaric hypoxia, and amyloid peptides-induced cognitive decline in rat and mice models, which was evaluated by Morris Water Maze Test [10, 30, 48-50]. Besides, the combined extract of *C. rotundus* and *Zingiber officinale* enhanced cholinergic function and decreased neurodegeneration and oxidative stress in a rat model of spatial memory impairment [49].

Acetylcholinesterase (AChE) inhibitory activity of C. rotundus

Acetylcholinesterase Inhibitors (AChEIs) inhibit the enzymatic elimination of acetylcholine, increasing its concentration at the postsynaptic membrane. AChEIs are beneficial in improving cholinergic system deficits and are used as cognitive enhancers in AD. Sharma and Gupta [51] reported the AChE inhibitory activity of the methanolic extract of *Cyperus*. The extract at 0.5 mg/mL showed 50% inhibition of electrophorus electricus (electric eel) AChE. It also strongly inhibited AChE from leaves of wheat rather than tomato. The extract also inhibited seed germination, root and shoot length. These properties explain the potential neuroprotective activity and a war against plants and herbivore animals growing in the same habitat.

Neuro-oxide-nitrosative and neuronal apoptosis inhibitory properties of C. rotundus

Oxide-nitrosative stress and apoptosis are the central phenomena of various diseases, including nervous system-associated illnesses [52, 53]. The brain is a vital organ in the biological system and is highly susceptible to oxide-nitrosative stress and apoptosis. Various reports demonstrated the anti-oxidant and anti-apoptotic effects of *C. rotundus* and its metabolites. We also observed that *C. rotundus* hydroalcoholic fractions exhibit neuro oxide-nitrosative and apoptosis inhibitory properties against H_2O_2/SIN-1 induced oxide-nitrosative stress and apoptosis in vitro in SH-SY5Y cells and restore anti-oxidant decline, inhibits ROS, inducible Nitric Oxide Synthase (iNOS), heat shock protein 70 (Hsp70), an anti-oxidant and anti-apoptosis protein expression, DNA damage and mitochondrial membrane potential [11, 54] (Figures 3 and 4). In another study, we demonstrated that the TOF fraction of *C. rotundus* also inhibited

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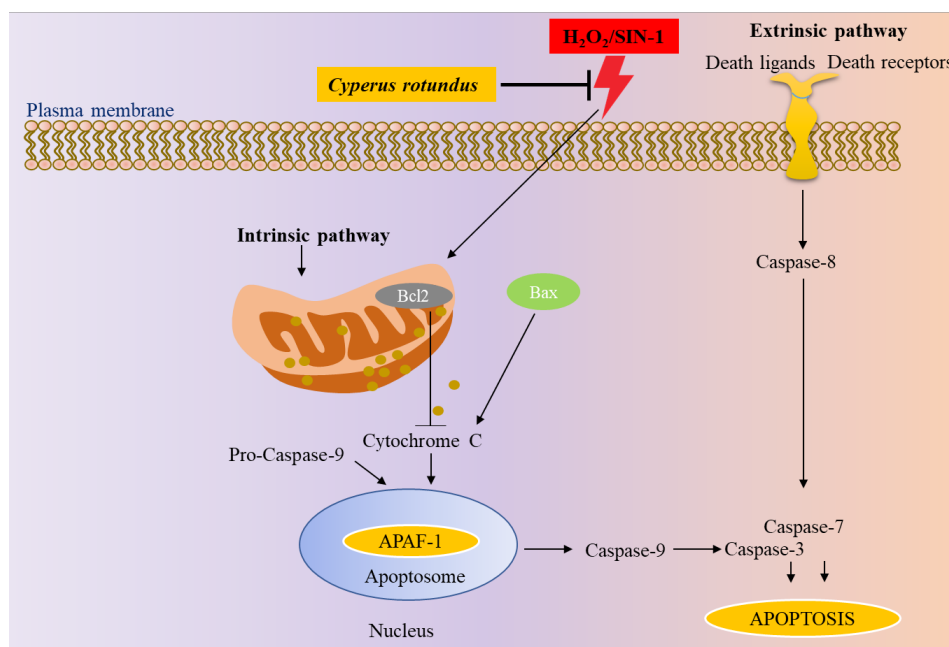
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Figure 4. Cyperus rotundus Inhibiting H2O2/SIN-1-Mediated apoptosis and Mitochondrial Damage, Intrinsic and Extrinsic Apoptosis The step that commits cells to undergo apoptosis is permeabilization of the mitochondrial outer membrane (MOMP), decrease in mitochondrial membrane potential, and increase in mitochondrial ROS and neurodegeneration.

in vivo hypobaric hypoxia-induced neuronal ROS, LDH (lactate dehydrogenase) release, and improved anti-oxidant decline, and regulated HIF-1α (Hypoxia-inducible factor 1-alpha), vascular endothelial growth factor (VEGF), and glial fibrillary acidic protein (GFAP) expression in vivo [55] (Figure 5).

Other Pharmacological Properties of C. rotundus

Anti-bacterial Property

Bacterial infections pose a risk to humans, and anti-bacterial agents suppress the growth and the ability of bacteria to reproduce [56]. Sini and Malathi [57] reported that hexane and water extracts of *Cyperus* tubers are potent inhibitors against Bacillus pumilis as determined by the zone of inhibition. Nima et al. [58] reported the antimicrobial activity of the oil extracted from fruits of *Cyperus* against Gram-positive bacteria, such as Staphylococcus aureus, compared to Gram-negative bacteria. The extract consists of cyperol, caryophyllene, cyperene, rotundine, and cyperone, which may be the active constituents responsible for the anti-bacterial activity of *Cyperus* oil extract. Kilani et al. [59] reported the anti-bacterial activity of different constituents of rhizome extract of *Cyperus*, which was further verified by Kilani-Jaziri et al. [60] in terms of both MIC (minimum inhibi-

tory concentration) and MBC (minimum bactericidal concentration) assays. Tambekar et al. [61] reported the anti-bacterial activity of *Cyperus* rhizome extract by the zone of inhibition assay.

Anti-oxidant Property

Several diseases are associated with oxidative stress, and anti-oxidant supplements/herbs inhibit/delay the disease progression and ameliorate the ROS-induced injury [13, 27]. Kilani et al. [62] reported that ethyl acetate, methanol, and TOF fractions of *Cyperus* tuber extract are potent scavengers of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. Nagulendran et al. [63] reported the anti-oxidant activity of ethanolic extract of *Cyperus* tubers by in vitro free radical scavenging assays. The extract efficiently scavenged superoxide, nitric oxide, hydroxyl radicals and also inhibited the lipid peroxidation induced by ferrous ions. These activities may account for the high polyphenolic content of the *Cyperus* extract. Kilani et al. [64] reported that the TOF fraction from tubers of *Cyperus* is a potent inhibitor of superoxide radicals than other fractions. In contrast, Jazari et al. [60] reported that ethyl acetate fraction is the most potent scavenger of superoxide radical among other fractions from aerial parts of *Cyperus*. These anti-oxidant activities were attributed to the high content of polyphenols, flavonoids, tannins, and sterols.

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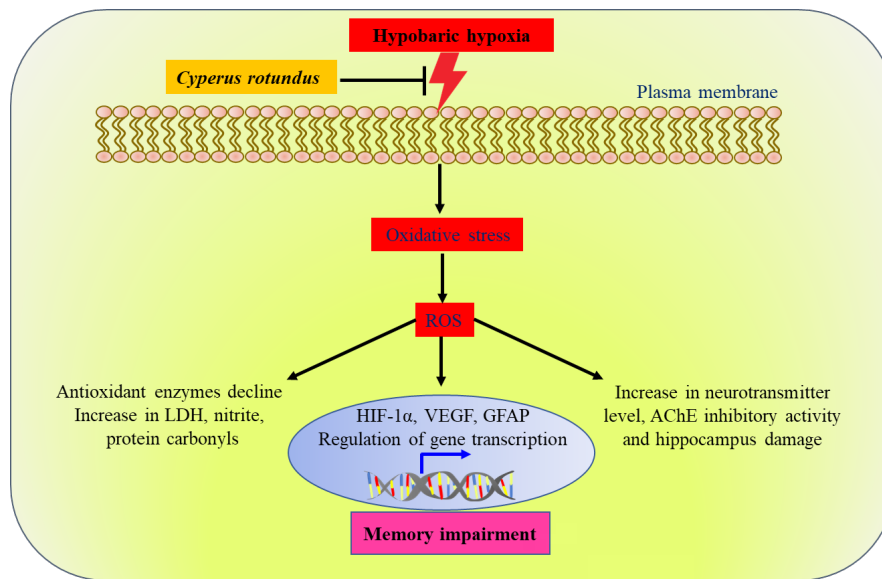
Figure 5. Hypobaric Hypoxia-Induced Oxide-Nitrosative Stress Mediating the Cognitive Impairment Modulating Effects of C. rotundus.

Anti-platelet property

The clumping of platelets in the blood leads to blood clots and coagulation, which is commonly seen in injury and is critical for hemostatic plug formation and thrombosis. However, platelet aggregation is also seen in cardiovascular diseases. Seo et al. [65] described the anti-platelet activity of *Cyperus* ethanolic extract (CRE) and its active compound nootkatone in an in vitro model of rat platelet aggregation and ex vivo mice tail bleeding model. CRE extract at 300 μg/mL inhibited the platelet aggregation challenged by collagen, thrombin, and arachidonic acid. Nootkatone at 30 mg/mL inhibited isolated rat platelet aggregation and increased the bleeding time up to 3 folds suggesting the potential application of the extract in arterial thrombosis.

Anti-diabetic property

Diabetes is one of the major leading causes of death worldwide. It is due to impairment in insulin production by the pancreas that leads to abnormal metabolism of carbohydrates with elevation in glucose levels. Several herbal treatments are recommended for this chronic disease. Karkala et al. [66] reported the significant anti-diabetic activities by gallic acid and quercetin compounds from C. *rotundus*. In silico docking studies by Lydia and Sudarsanam [67] found a novel compound, 15-hydroxy-4-oxo-10-pentadecanoic acid lactone, that possesses anti-diabetic property. Singh et al. [68] evaluated the activity of ethanolic extract of *Cyperus rotundus* rhizomes

and showed a decrease in enzyme activities, cholesterol, and triglyceride levels in Streptozotocin (STZ)-induced diabetic mice.

Anti-obese and hypolipidemic property

Obesity is due to excessive fat and overweight, and such a condition puts the individual at higher risk for other diseases, such as type 2 diabetes, cardiovascular disease, and cancer. Bambhole et al. [69] reported the effect of *Cyperus* extract (CR) by in vitro and in vivo studies on adipose tissue metabolism. CR extract treatment alone significantly released Lipolytic Glycerol (LG) and Free Fatty Acids (FFA), but CR extract combined with epinephrine resulted in a two-fold increase of LG and FFA release from adipose tissue cells. Further oral administration of the extract to rats also released plasma glycerol and FFA and inhibited the release of plasma phosphate, an indicator of Adenosine Monophosphate Kinase (AMPk) mediated lipolytic pathway.

In an elegant study, Lemaure et al. [6] reported the anti-obese activity of hexane extract of *Cyperus* in obese Zucker rats and β-adrenergic receptor-expressing 3T3-F422 adipocytes, where the β-3AR activation leads to weight loss by decreasing fat level. The rats showed 2.7% and 4.2% decline in body weight without effect on food intake of the animals with 45 mg/kg and 220 mg/kg of hexane extract administration, respectively, for 60 days, and the extracts had no toxicity up to 1 g/kg body weight. The triglyceride levels were markedly increased

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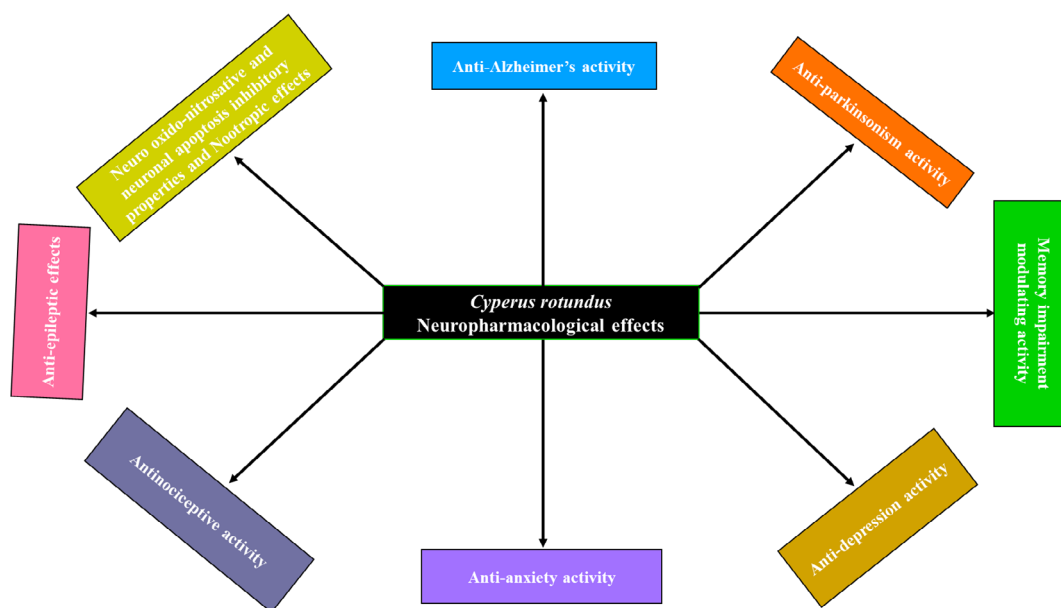
Figure 6. Graphical abstract: Neuropharmacological effects of Cyperus rotundus

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with a 220 mg/kg dose of extract. Further, the lipolytic activity of the extract was evaluated in adipocytes by measuring the β-AR binding assay by radiolabelling, whereas 250 μg/mL of hexane extract showed a 2.5 fold increase in lipolytic activity as well as β-3AR activation leading to energy expenditure by brown adipose tissue thermogenesis showing the potential anti-obese activity of hexane extract of *Cyperus* tubers.

Anti-tumor/carcinogenic property

In cancer, cells divide uncontrollably and destroy the body tissue. Several herbs and supplements are used as a natural treatment for cancer therapy. Kilani-Jaziri et al. [26] reported that the Ethyl Acetate (EA) and TOF enriched extracts inhibit K562 erythroleukemia cells. The inhibition of K562 cell proliferation might be due to apoptosis induction and activation of Phosphatidylinositol-3-Kinase (PI3K) and Mitogen-Activated Protein Kinases (MAPKs). Ethanol extract of *C. rotundus* showed anti-proliferative activity on human breast carcinoma MDA-MB-231 cells. It was associated with the induction of apoptosis by death receptors and survivin and Bcl-2 activity [70]. Nam et al. [71] revealed that hexane fraction of valencene from C. *rotundus* had therapeutic effects on UV-induced photoaging and decreased the melanin content after UVB irradiation in murine B16F10 melanoma cells. Amentoflavone reduced uterine tumors in rats. This mechanism might be due to higher Bax protein expression, reduced expression of Bcl-2, and progesterone-mediated apoptosis in uterine fibroid cells [72]. The methanolic extract of C. rotundus rhizome had

a cytotoxic effect on different cancer cell lines ranging from 4.52±0.57 to 9.85±0.68 μg/mL, and its inhibitory effect was shown by migration assay [73]. The n-hexane fraction of an ethanol extract from *C. rotundus* (6-acetoxy cyperene) is an anti-tumor compound that causes caspase-dependent apoptosis to inhibit cell growth in ovarian cancer and endometrial cancer cells [74].

Immunomodulatory and anti-allergic property

Inflammation is the body's defense mechanism to the external noxious physical or chemical stimuli triggered by invading pathogens and is a critical component of various pathological events [55]. Seo et al. [65] reported the anti-inflammatory activity of methanolic extract of *Cyperus* tubers by in vitro murine macrophage cell line RAW 264.7 model challenged with the endotoxin from Gram-negative bacteria, i.e., lipopolysaccharide. The cells showed characteristic features of inflammation, such as the release of nitric oxide by overexpression of iNOS and H_2O_2 radical production. Here the authors demonstrated the protective activity of *Cyperus* extract on endotoxin-induced nitric oxide expression, where 100 μg of the methanolic extract efficiently suppressed iNOS protein and mRNA overexpression and also exhibited anti-oxidative property and suppressed the free radicals suggesting the anti-inflammatory activity of methanolic extract of *Cyperus rotundus*. Dang et al. [75] further reported the anti-inflammatory activity of *Cyperus rotundus* tuber water extract in an in vivo model of carrageenan-induced paw edema and acetic acid-induced peritonitis. Furthermore, 270 mg/kg dose

of the extract showed 9.5% inhibition of the paw edema, and 390 mg/kg dose of extract inhibited the acetic acid-induced peritonitis.

In another study, Jin et al. [76] reported the anti-allergic activity of constituents isolated from *Cyperus*, namely valencene, nootkatone, caryophyllene α-oxide, β-pinene, 1,8-cineole, limonene, and 4-cymene by fractionation on rat basophilic leukemia-1 (RBL-1) cells and in an animal model of delayed-type hypersensitivity. Valencene, nootkatone, and caryophyllene α-oxide showed inhibition of cysteinyl leukotrienes by 60%, 93%, and 99 %, respectively, in calcium ionophore A23187 challenged RBL-1 cells. In another model, RBL-2H3 cells were sensitized by anti-DNP and treated with dinitrophenyl BSA (bovine serum albumin), released β–hexosaminidase by degranulation, which is a biomarker of allergy. *Cyperus* ethanolic extract at 300 μg/mL inhibited the degranulation by 21%, whereas the sesquiterpene valencene at 100 μM showed 88% inhibition. In mast cells, Lyn phosphorylation is the critical event in receptor-mediated degranulation. Lyn phosphorylation was measured by western blotting in degranulated RBL-2H3 cells, where 300 μg/mL CRE and 50 μM valencene inhibited the Lyn activation. Besides, the anti-allergic activity was evaluated in the hapten-treated mouse delayed hypersensitivity model, where the CRE extract, sesquiterpenes valence, and nootkatone reduced the ear thickness.

Recently, Tsoyi et al. [7] evaluated the anti-inflammatory activity of CRE and its isolated constituents in RAW 264.7 cells and mice model of sepsis. The authors found overexpression of Heme Oxygenase-1 (HO-1) with ethanolic extract, isolated compounds of *Cyperus*, namely nootkatone, valencene, β-selinene, α-cyperone, also downregulated iNOS expression in endotoxin-treated macrophages. The overexpression of HO-1 plays a pivotal role as cytoprotective, anti-apoptotic, and immunomodulator in various stresses. A similar trend was observed in the down-regulation of iNOS expression by nootkatone, valencene, and ethanolic extracts in HO-1-silenced, and LPS-challenged (lipopolysaccharide) cells, suggesting that anti-inflammatory effect is mediated by HO-1 upregulation. Overexpression of cytokine, high mobility group box 1 protein (HMGB1) plays a critical role in sepsis-induced death. In contrast, the downregulation of HMGB1 expression with LPS challenge by HO-1 upregulation was observed with nootkatone, valencene, and ethanolic extracts. Also, it increased the survival rates of Cecal Ligation and Puncture (CLP)-induced sepsis in mice.

Anti-malarial property

Malaria is a life-threatening mosquito-borne blood disease caused by parasites transmitted to people. Traditional medicines have been used as anti-malarial therapy by tribal and folklore medicine. Thebtaranonth et al. [77] explored the anti-malarial activity of *C. rotundus*. Among tested compounds, 10, 12-peroxycalamenene had a maximum effect with an EC50 of 2.33 × 10−6 M and dichloromethane extract with an IC50 between 10 and 50 μg/mL [78, 79].

Anti-diarrheal property

Diarrhea is a leading cause of malnutrition and death in children under five years old. Traditional medicine is popular for the treatment of acute diarrhea. The anti-diarrheal activity of different fractions (methanolic and petroleum ether) of *C. rotundus* rhizome exhibited significant activity in castor oil-induced diarrhea in mice [80]. Daswani et al. [81] studied the role of decoction of *C. rotundus* against diarrhea and in the absence of antimicrobial activity due to the mechanism of bacterial virulence. Venkatasubramanian et al. [82] reported 46% inhibition of the diarrheal activity of methanolic extract of *C. rotundus*.

Gastroprotective property

Gastroprotective agents protect the stomach and gastric system from various forms of ulcers and gastric tissue damage. Guldur et al. [83] reported the gastroprotective effect of methanolic extract of *Cyperus* rhizomes in a model of an ischemia-reperfusion-induced stomach injury. The administration of the extract effectively restored the anti-oxidant status measured by glutathione and lipid peroxidation products and also protected the microvillus architecture of the stomach with the ischemic model but to a lesser extent in the ischemia-reperfusion model, explaining the potential gastroprotective effect of the extract.

Protein oxidation and protein nitration prevention property

The excess amount of ROS in the presence of •NO or •NO-derived metabolites leads to the formation of nitrating species such as peroxynitrite [20, 84]. The protein oxidation and nitration of tyrosine residues to 3-nitro-tyrosine disrupt nitric oxide (•NO) signaling towards pro-oxidant processes and alters the metabolism [85]. Ardestani and Yazdanparast et al. [86] observed that extracts of *C. rotundus* suppresses AGE formation in a fructose-mediated protein glycoxidation model in vitro and inhibit oxidative stress. We also determined that *C. rotundus* inhibits SIN-1 induced protein nitration and

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AAPH-induced protein oxidation in both in vitro and ex-vivo models [13, 54] (Figure 6).

Pharmacological Effects of C. Rotundus On Human Subjects/Human Cell Lines

Humans consume a wide variety of herbs, spices, and vegetables along with animal and dietary products as part of the diet, which play a key role in maintaining the well-being of an individual. Various herbal and food products are demonstrated to possess medicinal values. In a previous study, *C. rotundus* aqueous extract was shown to have anti-inflammatory activity for conjunctivitis in human subjects [87]. In another study, Appaji et al. [88] investigated the immunoglobulin-enhancing effects of Bala compound, a combination of several plants along with *C. rotundus*. The orally administered Bala compound enhanced immunoglobulin content in infants compared with the multivitamin supplementation group suggesting the potential immunomodulatory activity of the plant extract. Recently, we evaluated the neuroprotective effects of *C. rotundus* against oxidative stress-mediated neuronal damage of SH-SY5Y human neuronal cells [11, 54].

Conclusion and Future Perspectives

The common neurological diseases affecting people across the globe include Alzheimer, Parkinson, epilepsy, ischemia, and its associated neurodegeneration with cognitive decline. *C. rotundus* is a weed, but it is identified to possess various pharmacological properties, including neuro-pharmacological activities. The root part of the plant has been extensively used as a traditional medicine to cure various ailments and used to develop nutraceuticals and pharmacological products. The advancement of scientific methodologies and various in vitro and in vivo preclinical animal models determined the pleiotropic activities of mustaka and its constituents as ethnomedicine. Although various metabolites of *C. rotundus* have been identified, only a few have been thoroughly investigated for the molecular mechanism/mode of action. *C. rotundus* has also been used in combination with other plants as a combinational therapy to treat several diseases. The reported cytotoxic/toxicological effects of *C. rotundus* should be taken into account. However, a little investigation has been carried out on the pharmacokinetic and pharmacodynamic properties of mustaka and its chemical constituents. Furthermore, the full utility of this plant will be more beneficial in the coming years and has great potential for use in the pharmaceutical industry. The phytochemistry of biochemical constituents of *C. rotundus* from various researchers across the globe by various analytical techniques demonstrated the genetic diversity of the plant-based on its cultivation in different agro-climatic zones. Furthermore, pharmacokinetics, pharmacodynamics, bioavailability, and pharmacognosy studies are warranted for confirming the phytochemicals responsible for various pharmacological actions and their method and mode of action at the molecular and cellular level and clinical safety in humans.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

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