Phytochemistry Reviews
https://doi.org/10.1007/s11101-023-09870-3

Phytochemistry, data mining, pharmacology, toxicology and the analytical methods of *Cyperus rotundus* L. (Cyperaceae): a comprehensive review

Bian-Xia Xue · Ru-Shang He · Jia-Xin Lai · Nana Ama Mireku-Gyimah · Li-Hua Zhang · Hong-Hua Wu

Received: 30 May 2022 / Accepted: 12 April 2023

Abstract *Cyperus rotundus* L. has been widely used in the treatment and prevention of numerous diseases in traditional systems of medicine around the world, such as nervous, gastrointestinal systems diseases and inflammation. In traditional Chinese medicine (TCM), its rhizomes are frequently used to treat liver disease, stomach pain, breast tenderness, dysmenorrheal and menstrual irregularities. The review is conducted to summarize comprehensively the plant's vernacular names, distribution, phytochemistry, pharmacology, toxicology and analytical methods, along with the data mining for TCM prescriptions containing *C. rotundus*. Herein, 552 compounds isolated or identified from *C. rotundus* were systematically collated and classified, concerning monoterpenoids, sesquiterpenoids, flavonoids, phenylpropanoids, phenolics and phenolic glycosides, triterpenoids and steroids, diterpenoids, quinonoids, alkaloids, saccharides and others. Their pharmacological effects on the digestive system, nervous system, gynecological diseases, and other bioactivities like antioxidant, anti-inflammatory, anti-cancer, insect repellent, anti-microbial activity, etc. were summarized accordingly. Moreover, except for the data mining on the compatibility of *C. rotundus* in TCM, the separation, identification and analytical methods of *C. rotundus* compositions were also systematically summarized, and constituents of the essential oils from different regions were re-analyzed using multivariate statistical analysis. In addition, the toxicological study progresses on *C. rotundus* revealed the safety property of this herb. This review is designed to serve as a scientific basis and theoretical reference for further exploration into the clinical use and scientific research of *C. rotundus*.

Bian-Xia Xue, Ru-Shang He, Jia-Xin Lai have contributed equally to this work and should be considered co-first authors.

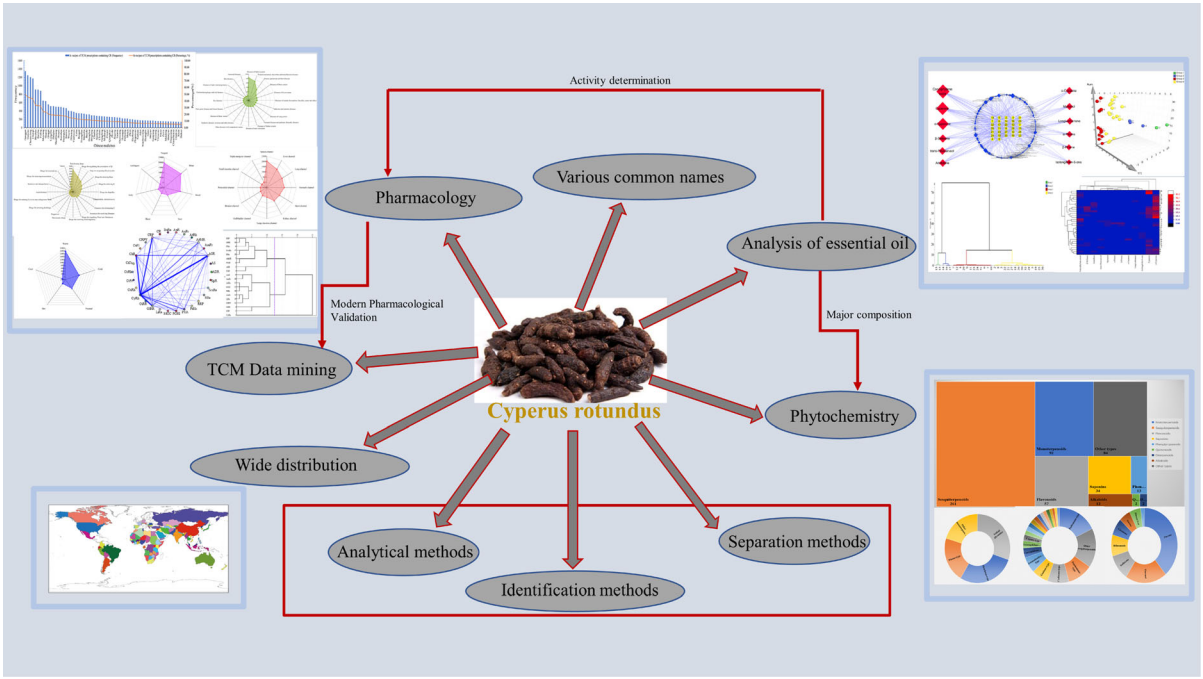
Supplementary Information The online version contains supplementary materials available at https://doi.org/10.1007/s11101-023-09870-3.

B.-X. Xue · R.-S. He · J.-X. Lai · L.-H. Zhang · H.-H. Wu (✉)
State Key Laboratory of Component-Based Chinese Medicine, Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, 10 Poyanghu Road, West Area, Tuanbo New Town, Jinghai District, Tianjin 301617, People's Republic of China
e-mail: wuhonghua2011@tjutcm.edu.cn

N. A. Mireku-Gyimah
Department of Pharmacognosy and Herbal Medicine, School of Pharmacy, College of Health Sciences, University of Ghana, Legon-Accra, Ghana

Published online: 15 May 2023

Graphical Abstract



Keywords *Cyperi rhizome* · Association rules · Gynecological diseases · Sesquiterpenoids · Essential oil · GC–MS

Abbreviations

CyRh	*Cyperi rhizoma*
TCM	Traditional Chinese medicine
CMs	Chinese medicines
ChP	Chinese Pharmacopoeia
EOCR	The essential oil of *C. rotundus*
TLC	Thin-layer chromatography
PTLC	Preparative thin-layer chromatography
HPTLC	High-performance thin-layer chromatography
MPLC	Medium pressure liquid chromatography
HPLC	High performance liquid chromatography
PHPLC	Preparative high-performance liquid chromatography
UHPLC	Ultra-high performance liquid chromatography
SFE	Supercritical fluid extraction
HSCCC	High-speed counter-current chromatography
UFLC-MS^n	Ultra-fast liquid chromatography mass spectrometry
HR-MS	High resolution mass spectrometry
NMR	Nuclear magnetic resonance
HD	Hydrodistillation
SPME	Solid phase micro extraction
PLE	Pressurized liquid extraction
HR-ESI–MS	High resolution-electrospray ionization mass spectrometry
EI-MS	Electron impact mass spectrometry
FAB-MS	Fast atomic bombardment mass spectrometry
Q-TOF–MS	Quadrupole-time of flight mass spectrometry
MS–MS	Tandem mass spectrometry
UHPLC-QTOF-MS	Ultra-high performance liquid chromatography quadrupole-time of flight mass spectrometry
GC–MS	Gas chromatography-mass spectrometry
GC	Gas chromatography

GC-FID	Gas chromatography-flame ionization detector
GC-O-MS	Gas chromatography–olfactometry-mass spectrometry
PDA	Flame ionization detector
DAD	Diode array detection
UV	Ultraviolet–visible spectra
IR	Infrared spectra
PIXE	Particle induced X-ray emission
ICP-MS	Inductively coupled plasma mass spectrometry
HCA	Hierarchical clustering analysis
PCA	Principal component analysis
CD	Circular dichroism
COVID-19	Coronavirus disease 2019
TOF	Total oligomeric flavonoid
TPC	Total phenolic
DPPH	1,1-Diphenyl-2-picrylhydrazyl
SOD	Superoxide dismutase
HO-1	Heme oxygenase-1
GSH-Px	Glutathione peroxidase
MDA	Malondialdehyde
PTZ	Pentylentetrazole
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
5-LOX	5-Lipoxygenase
COX-2	Cyclooxygenase-2
PGE2	Prostaglandin E2
IL-1	Interleukin 1
IL-6	Interleukin 6
TNF-α	Tumor necrosis factor-α
NF-κB	Nuclear factor-kappa B
iNOS	Nitric oxide synthase
LPS	Lipopolysaccharide
TPA	12-*O*-Tetradecanoylphorbol-13-acetate
NO	Nitric oxide
TST	Tail suspension test
FST	Forced swimming test
HBV	Hepatitis B virus
DCFH	2,7-Dichlorofluorescein
EtOAc	Ethyl acetate
EECR	Ethanol extract of *C. rotundus*
MECR	Methanolic extract of *C. rotundus*
CYP450	Cytochrome P450
ROS	Reactive oxygen species
AD	Alzheimer's disease
CNS	Central nervous system
H_2O_2	Hydrogen peroxide
ABTS	2,2′-Azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
AChE	Acetylcholinesterase
MAO	Monoamine oxidase
MIC	Minimum inhibitory concentration
MBC	Minimum bactericidal concentration
LD_{50}	Median lethal concentration and median lethal dose
EC_{50}	Concentration for 50% of the maximal effect
CC_{50}	The 50% cytotoxic concentration
IC_{50}	Half maximal inhibitory concentration
BMI	Body mass index
GABA	γ-Aminobutyric acid
AP-1	Activator protein-1

Introduction

Cyperus rotundus L. (family: Cyperaceae), an erect, glabrous, grasslike, fibrous-rooted, herbaceous plant with slender, scaly creeping rhizomes, is widely distributed in temperate, tropical and sub-tropical regions, such as China, India, South Africa, Korea, Japan, Egypt, Iran and other countries (Chang et al. 2012; Aeganathan et al. 2015; Liu et al. 2016; Janaki et al. 2018; Sabir et al. 2020). *C. rotundus* has a long history as an herbal remedy in several nations, and accordingly has been collated into the native medical systems in various countries and prefectures. In China, the rhizomes of *C. rotundus* officially referred to as "Xiangfu" (*Cyperi rhizoma*, CyRh) according to the 2020 Edition of Chinese Pharmacopoeia (ChP) and initially recorded in "*Mingyi Bielu*", is a gynecological herb commonly used in Traditional Chinese Medicine. And it is frequently recommended for the treatment of epigastric pain, breast aches, irregular menstruation, dysmenorrhea and amenorrhea (Chinese Pharmacopoeia Committee of China, Edition 2020). In India Ayurveda, *C. rotundus*, also known as "Motha" and "Mutha", is used for the treatment of diarrhea, dysentery, diabetes, arthritis, leprosy, bronchitis, amenorrhea, dysmenorrhea, fever and blood disorders (Babiaka et al. 2021). In West Asia, *C. rotundus* is applied in folk medicine for the treatment

of leprosy, fever, thirst and blood illnesses. In Egypt, *C. rotundus* is used in traditional medicine as an anthelmintic, aphrodisiac, diuretic, sedative, carminative, stimulant and tonic, and for treating renal colic and stomach pains (Samra et al. 2020). Apart from the above, *C. rotundus* also is the raw material of some perfumes and mosquito repellents.

Till now, the presence of monoterpenoids (menthane-, pinane-, iridoid glycosides, etc.), sesquiterpenoids (eudesmane-, patchoulane-, cadinane-, guaiane-, aromodendrane-, eremophilane-, caryophllane-, rotundane-, etc.), flavonoids (flavone-, flavonol-, isoflavone-, biflavonoids-, etc.), phenylpropanoids (simple phenylpropanoids-, coumarins-, and lignans-), phenolics and phenolic glycosides, triterpenoids and steroids, diterpenoids, quinonoids, alkaloids, saccharides and other constituents in *C. rotundus* has been amply demonstrated by a large number of phytochemistry investigations (Sivapalan 2013; Pirzada et al. 2015; Kabir and Abbasi 2018). Essential oil is the indispensable substance contained in the rhizomes, tubers and aerial parts of *C. rotundus*, and it provides the characteristic odor and flavor of this herb (Zoghbi et al. 2008; Kilani-Jaziri et al. 2009; Chang et al. 2012). Moreover, the major constituents, such as α-cyperone, α-rotunol, *β*-rotunol, cyperotundone, cyperene, nootkatone, and isocyperol, were frequently described to be isolated from the essential oil and the extracts of *C. rotundus* rhizomes (Sivapalan 2013; Sonwa and König 2001; Ahn et al. 2015; Xu et al. 2015).

Extensive modern pharmacological evidences have revealed that *C. rotundus* possesses a variety of biological activities including neuroprotective (Jebasingh et al. 2014; Dabaghian et al. 2015), anti-inflammatory (Rocha et al. 2020), antipyretic (Deng et al. 2012), analgesic (Ahmad et al. 2012), sedative (Srivastava et al. 2013), anticonvulsant (Khalili et al. 2011), gastroprotective (Thomas et al. 2015), anthelmintic (Al-Massarani et al. 2016; Janaki et al. 2018), antidiarrheal (Uddin et al. 2006; Daswani et al. 2011), anti-cancer (Saad et al. 2018; Susianti et al. 2018), anti-obesity (Majeed et al. 2022), antioxidant (Khalili et al. 2011), anti-bacterial (Ahmad et al. 2012), anti-malarial (Thebtaranonth et al. 1995), anti-diabetic (Singh et al. 2015), wound healing (Puratchikody et al. 2006; Srivastava et al. 2013), anti-cytotoxic (Sayed et al. 2007), anti-depressant (Lin et al. 2015; Hao et al. 2017), anti-HBV (Parvez et al. 2019), and lactogenic (Badgujar and Bandivdekar 2015) activity.

In the past decades, several reviews related to *C. rotundus* have been published. However, most of them focused on the traditional uses, phytochemistry and pharmacological aspects (Sivapalan 2013; Pirzada et al. 2015; Al-Snafi 2016; Kumar et al. 2017; Bajpay et al. 2018; Kabir and Abbasi 2018; Kamala et al. 2018; Babiaka et al. 2021; Kandikattu et al. 2021; Bezerra and Pinheiro 2022; Kandikattu et al. 2021; Lu et al. 2022; Rita Yadav et al. 2022). There is no comprehensive overview concerning the separation, identification and analytical techniques of the chemical components of *C. rotundus*, not to mention an in-depth data excavation of *C. rotundus*'s common compatibility with other Chinese medicines (CMs). For instance, Kumar et al. summarized *C. rotundus*'s traditional uses and pharmacological effects (Kumar et al. 2017). Medicinal applications, phytochemistry and pharmacology of *C. rotundus* were worked on (Sivapalan 2013; Pirzada et al. 2015; Kamala et al. 2018; Kandikattu et al. 2021). Plant morphology, distribution, phytochemical constituents and pharmacological activities of *C. rotundus* were focused on (Al-Snafi 2016; Bajpay et al. 2018; Kabir and Abbasi 2018). Babiaka et al. reported in detail the bioactivities and mechanisms involved in certain *C. rotundus* components (Babiaka et al. 2021). Lu et al. concentrated on an overall summary on the pharmacological effects of the chemical constituents and extracts in *C. rotundus* (Lu et al. 2022).

In this paper, a comprehensive literature investigation on *C. rotundus* was accomplished by retrieving a series of electronic databases, including PubMed, Google Scholar, SciFinder, ScienceDirect, Web of Science, Huabeing database, CNKI, Traditional Chinese Medicine Resource Network. This present overview intended to compile an overall knowledge on phytochemistry, pharmacology, separation, identification and analytical methods, as well as data mining of *C. rotundus*. Unlike previous reviews in phytochemistry and pharmacology, this paper goes further in the following aspects. To make the content more thorough, advances in phytochemistry, pharmacology and toxicology from 1941 to 2022 were reviewed, 552 chemical constituents isolated or identified from *C. rotundus* have been systematically collated and classified for the first time. And the pharmacological and toxicological studies of *C. rotundus* on the digestive system, nervous system and gynecological diseases and other activities have been summarized

accordingly. Moreover, the separation, identification and analytical methods of the chemical constituents of *C. rotundus* were systematically summarized for the first time. Furthermore, the chemical compositions of *C. rotundus* essential oils from different regions have been re-analyzed by multivariate statistical analysis. Additionally, data mining has been carried out for the first time on the compatibility of *C. rotundus* in TCM.

Distribution and synonyms

Owing to its adaptation to a broad range of soil textures, altitudes, climates, soil pH, and moisture levels, *C. rotundus*, commonly known as "The World's Worst Weed", may thrive in a variety of locations and ecosystems. It is unquestionably a global species, prospering in tropical, subtropical, and temperate regions and especially well in Asia, Africa, Europe and America. Table 1 gives a full summary of the regions where *C. rotundus* is located and Fig. 1 depicts colorfully its extensive distribution.

The wide distribution of *C. rotundus* throughout the world has given it a unique name in different regions. To facilitate a comprehensive investigation and research by future researchers, it is essential to provide a systematic summary involving a variety of vernacular names of *C. rotundus*. Table 2 thus provides a detailed summary of the diverse common names of *C. rotundus* used by different regions.

Data mining in TCM

In China, TCM prescriptions briefly refer to an orderly combination of CMs following the principles of CMs recipe (Sovereign and subject Musa acts) for the treatment of a specific disease under the guidance of TCM theory. *C. rotundus*, known as "Xiangfu" or "Xiangfuzi" in China which enrolled as "*Cyperi rhizome*" (CyRh) of Latin name in ChP, is dominantly native to the middle and lower reaches of the Yangtze River and the Huanghe River, with the optimum quality in Zhejiang and Shandong provinces. It was

Table 1 The distribution of *C. rotundus* around the world

Continent	Nation	References
Eastern Asia	China, Japan, Korea, India, Nepal, Pakistan, SriLanka, Myanmar, Thailand, Vietnam, Indonesia, Malaysia, Philippines	Lawal and Oyedeji (2009), Pirzada et al. (2015), Al-Snafi (2016), Yagi et al. (2016), Bajpay et al. (2018), Samra et al. (2020)
Africa	Algeria, Egypt, Libya, Morocco, Tunisia, Western Sahara, Chad, Djibouti, Eritrea, Ethiopia, Somalia, Sudan, Kenya, Tanzania, Uganda, Burundi, Equatorial, Guinea, Gabon, Rwanda, Democratic Republic of Congo, Benin, Burkina Faso, Cote D'Ivoire, Ghana, Guinea, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone, Togo, Angola, Malawi, Mozambique, Zambia, Zimbabwe, Botswana, Namibia, South Africa, Swaziland	
Middle Asia	Kazakhstan, Kyrgyzstan, Turkmenistan, Uzbekistan	
Western Asia	Afghanistan, Iran, Iraq, Saudi Arabia, Yemen, Palestine, Lebanon, Syria, Turkey	
Europe	Austria, Switzerland, Albania, Bulgaria, Croatia, Greece, Romania, Serbia, Slovenia, France, Portugal, Spain	
North America	United States of America (USA), Mexico	
Southern America	Brazil, Bolivia, Colombia, Ecuador, Peru, Argentina	
Caucasus	Armenia, Azerbaijan, Russian Federation	
Pacific	Marshall Islands, Micronesia, Northern Mariana Islands	

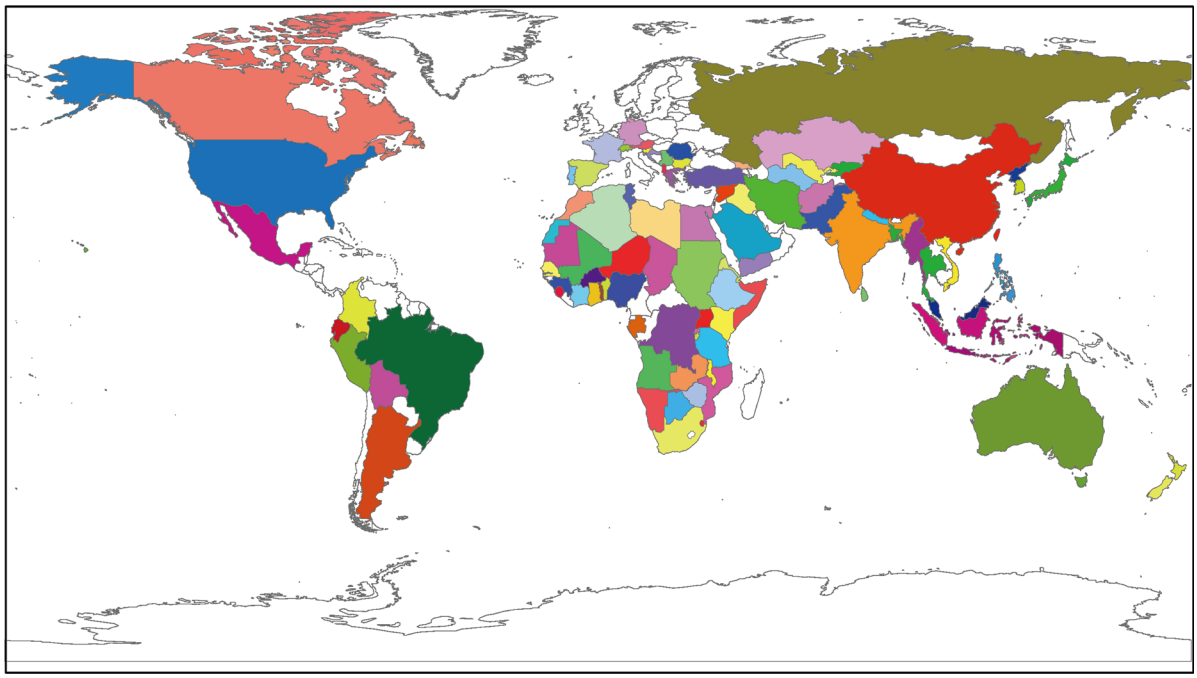


Fig. 1 The distribution of *C. rotundus* around the world. (The colours on the map were used only to distinguish between different countries)

originally recorded in the book "*Mingyi Bielu*" and possesses the effects of soothing liver-Qi stagnation and alleviating depression, regulating Qi for protecting the stomach as well as regulating menstruation and relieving menstrual pain, making it the most commonly available CM for regulating the flow of Qi to alleviate depression. In "*Compendium of Materia Medica*", it was described that Xiang Fu is 'the chief commander of the treatment for Qi diseases and the leading general of the treatment for female diseases', and it is frequently applied as a medicine for soothing liver-Qi stagnation and relieving depression. Since ancient times, it has been known as "holy medicine" in gynecology. At present, big data processing and analysis techniques, especially data mining and network pharmacology, have been greatly applied to the study of the material basis, mechanism of action and medication pattern of TCM. Therefore, data mining (Rao et al. 2021; Wang et al. 2021a; Xue et al. 2022) has been performed in this section on the TCM prescriptions containing raw CyRh or its processed product, in order to better explore the combination pattern characteristics of CyRh in TCM for better clinical application. The detailed materials and methods of data mining and comprehensive results have been presented in the supplementary materials.

The results showed that 2712 TCM prescriptions containing CyRh or its processed products were adopted, with 449 CMs enrolled in the ChP. The top 10 CMs with the greatest frequency in combination with CyRh were *Angelicae sinensis radix* (Danggui), *Glycyrrhizae radix et rhizome* (Gancao), *Chuanxiong rhizome* (Chuanxiong), *Citri reticulatae pericarpium* (Chenpi), *Paeoniae radix alba* (Baishao), *Atractylodis macrocephalae rhizome* (Baizhu), *Poria* (Fuling), *Aucklandiae radix* (Muxiang), *Amomi fructus* (Sharen), *Citri reticulatae pericarpium viride* (Qingpi) (Fig. 2a and supplementary Table S1). The CMs in combination with CyRh mostly fell into the effect classifications of tonic, regulating the circulation of Qi, invigorating Blood Circulation, clearing Heat and relieving Exterior syndrome (Fig. 2c, supplementary Table S3), with natures of Warm (Fig. 2d, supplementary Table S4), flavors of Pungent, Bitter as well as Sweet (Fig. 2e, supplementary Table S4), and channel tropisms of Spleen, Liver, Lung, Stomach, Heart and Kidney (Fig. 2f, supplementary Table S5). In traditional recipes of TCM prescriptions, CyRh is frequently used for treatments of diseases of (I) the

Table 2 Various vernacular names of *C. rotundus*

Language	Synonyms	References
Arabic	Sa'ed, Soadekufi	Lawal and Oyedeji (2009), Pirzada et al. (2015), Al-Snafi (2016), Kumar et al. (2017), Bajpay et al. (2018), Kabir and Abbasi (2018)
Chinese	Xiangfu, Suo cao, Xiang fu zi	
English	Nut grass, Purple nutsedge, Java grass, Rhizoma cyperi, Coco-grass, Ground-almond, Nut sedge, Nut-grass, Purple nut, Sedge, Purple nut-grass, Red nut sedge, Java-grass, Purple nut sedge	
Indian	Motha, Mutha, Musta, Nagagmotha, Nagarmothaya, Nagarmotha, Nagaramothaya, Keyabon, Korakizanna, Barik motha, Bimbal, Muthakasu, Varida, Koranari-gadde	
French	Souchet rond	
German	Knolliges Zypergras	
Italian	Zigolo infestante	
Japanese	Hamasuge	
Korean	Hyangbuja	
Portuguese	Alho-bravo, Capim-alho, Capim-dandá, Tiririca, Tiririca-vermelha	
Spanish	Castañuela, Cipero, Coquito, Juncia real	
Swedish	Nötag	
Burmese	Vomonniu	
Malayan	Mushkezamin	
Persian	Mushkzenezamin	
Sanskrit	Chakranksha, Charukesara	
Urdu	Saad kufi	

Spleen system, (II) women's menstrual, leucorrhea and miscellaneous diseases, (III) fetuses, parturients and their diseases and (IV) the Brain system and (V) the Liver system (Fig. 2b, supplementary Table S2), and is generally consistent with the results of modern pharmacological studies of CyRh in vivo and in vitro.

Association rules were provided by the Apriori algorithm as presented in Fig. 3 and supplementary Tables S6–S9. It has revealed the overall compatibility patterns of the core CMs in the TCM prescriptions containing CyRh in Fig. 3 and supplementary Table S6. The CMs combinations with the highest support were Xiangfu-Danggui, Xiangfu-Gancao, Xiangfu-Chuanxiong, Xiangfu-Chenpi, Xiangfu-Baishao, Xiangfu-Baizhu. Among them, the Danggui and Chuangxiong belong to drugs for invigorating blood circulation, Gancao, Baishao and Baizhu belong to tonics, while Chenpi is one of the CMs for regulating the circulation of Qi. The result suggested that Xiangfu (*C. rotundus*) may be commonly combined with CMs with efficacies of tonic, regulating the circulation of Qi, or invigorating Blood circulation in TCM prescriptions, basically in line with those results of the above frequency statistics and can be corroborated with each other.

Based on the association rules, among the various TCM clinical diseases treated by TCM prescriptions containing CyRh, the most common diseases of the Spleen system, women's menstrual, leucorrhea and miscellaneous diseases as well as fetuses, parturients and their diseases were selected for analysis of medication patterns.

The results demonstrated that in the traditional application for treating diseases of the Spleen system, the core combination of CMs was Mu Xiang Fen Qi recipe, with slight variations depending on the health condition of the patient (Fig. 3b, supplementary

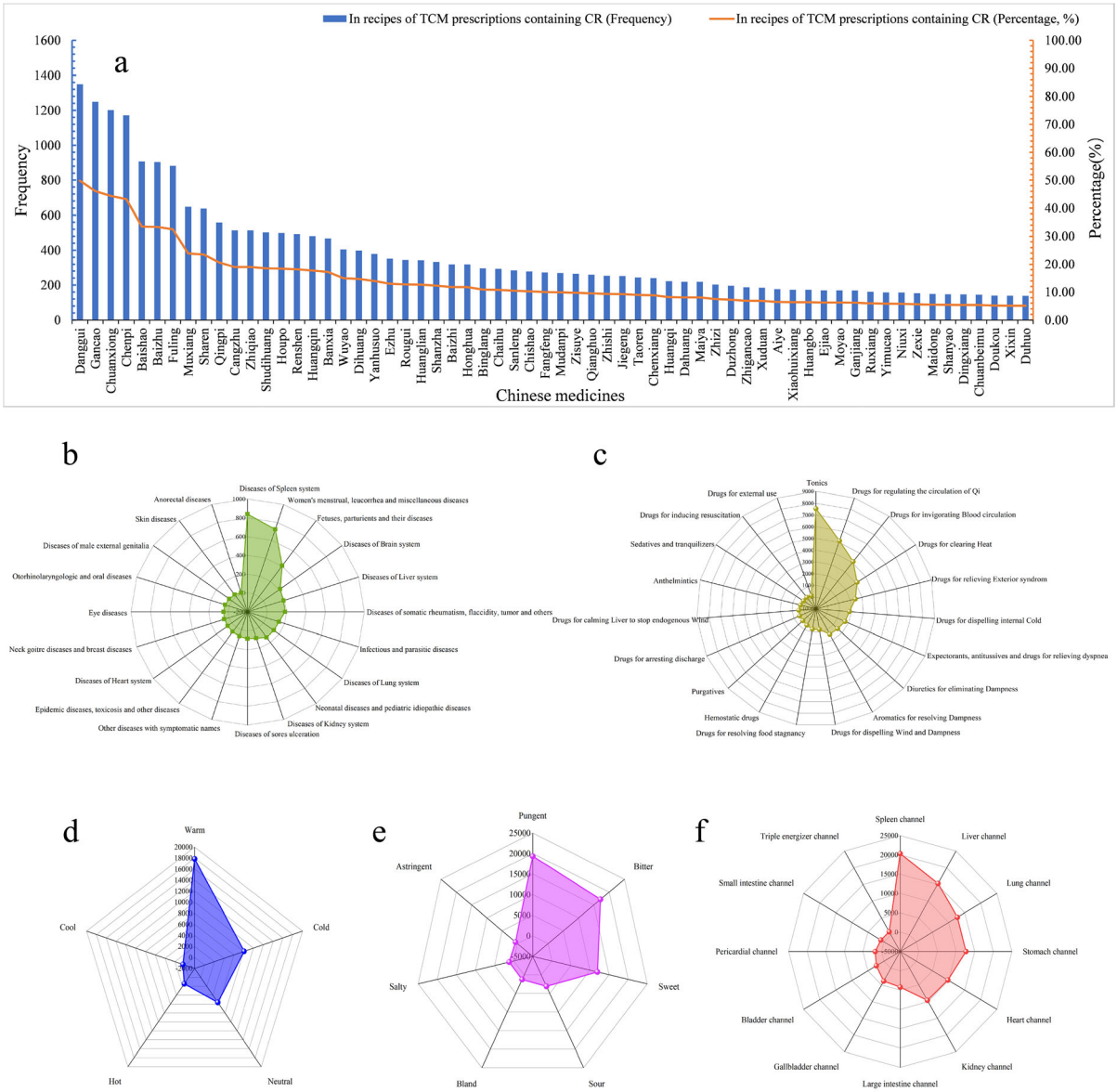


Fig. 2 The results of frequency statistics for the recipes of TCM prescriptions containing CyRh. **a** The CMs prescribed with frequency percentage above 5% excluding data of CyRh; **b** Indication classifications; **c** Effect classifications of the CMs prescribed excluding data of CyRh; **d** Natures of CMs prescribed excluding data of CyRh; **e** Flavors of CMs prescribed excluding data of CyRh; **f** Channel tropisms of CMs prescribed excluding data of CyRh

Table S7). The CMs combinations with the highest support were Xiangfu-Chenpi, Xiangfu-Gancao, Xiangfu-Muxiang, Xiangfu-Sharen, Xiangfu-Baizhu (Chenpi and Muxiang belong to CMs for regulating the circulation of Qi, Gancao and Baizhu belong to tonics, Sharen is one of the aromatics for resolving Dampness), revealing that in the treatment of spleen system diseases, Xiangfu (*C. rotundus*) is regularly compatible with CMs for regulating the circulation of Qi, tonics and aromatics for resolving Dampness. It is well known that Xiangfu, Chenpi, Muxiang, Sharen, and Baizhu all serve the spleen and stomach meridians in TCM. Gancao is usually applied as an adjuvant and dispatcher herb in TCM prescriptions to moderate the

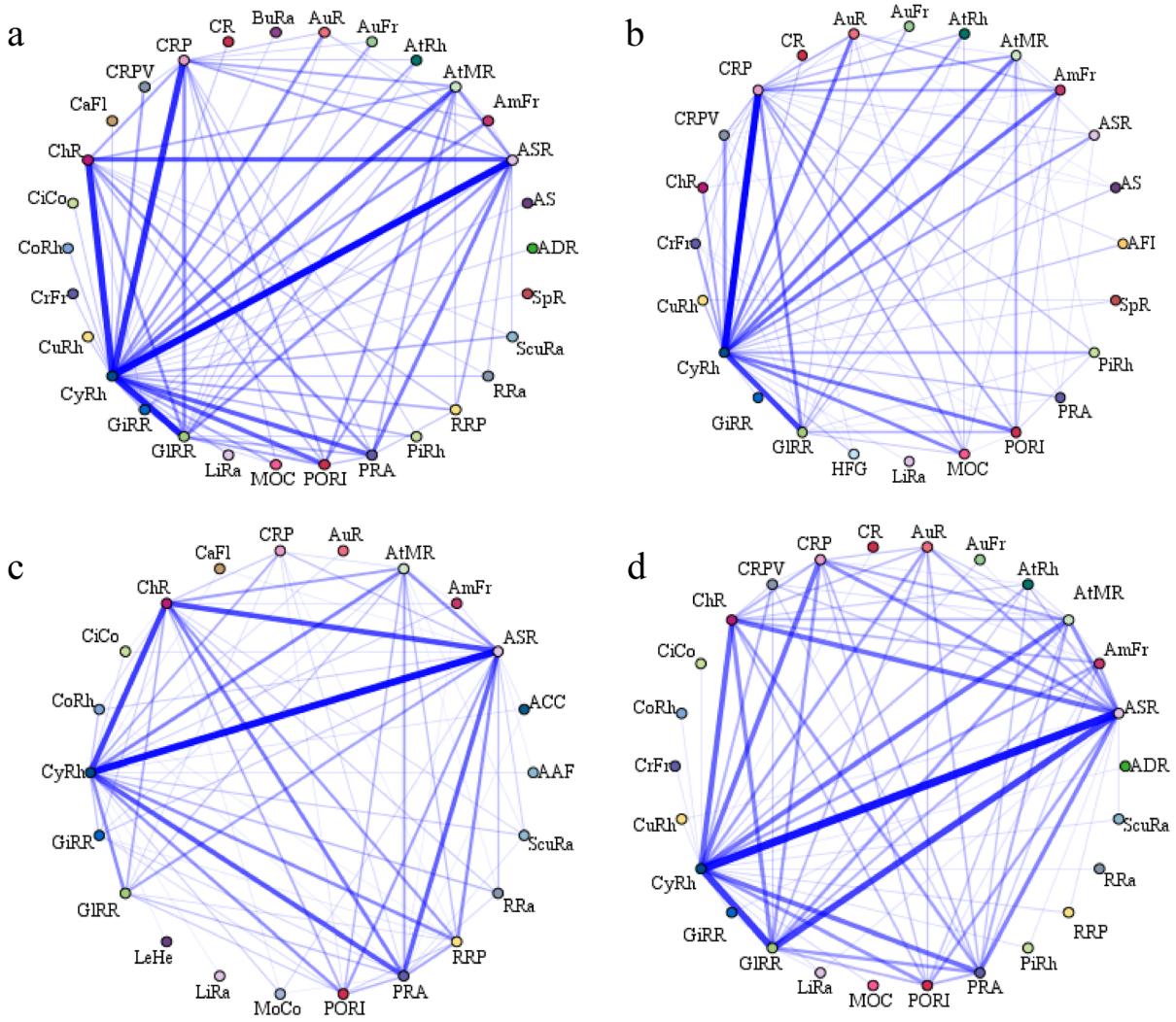


Fig. 3 Representative network display for association rules of the CMs in TCM prescriptions containing CyRh. **a** The CMs with high-frequencies; **b** The CMs prescribed for the Spleen system diseases; **c** The CMs prescribed for the women's menstrual, leucorrhea and miscellaneous diseases; **d** The CMs prescribed for the fetuses, parturients and their diseases

violent and irritant effects of medicines, and at the same time can strengthen the spleen. It is evident that the data mining results and the traditional uses of TCM both were mutually verified, explaining the reasonability and reliability of the data mining findings.

On the other hand, the outcomes of the association rules between women's menstrual, leucorrhea and miscellaneous diseases and fetuses, parturients and their diseases were extremely similar (Fig. 3c and d, supplementary Tables S8–9). And the core combination of CMs was Siwu Tang for curing both of their diseases in TCM. The association rule analysis results showed that the CMs combinations with the highest support were Xiangfu-Danggui, Xiangfu-Chuanxiong, Xiangfu-Baishao, Xiangfu-Shudihuang, Xiangfu-Baizhu, Xiangfu-Gancao (Shudihuang belong to tonics), which reveals that in the treatment of women's diseases, Xiangfu is often compatible with tonics and medicines for invigorating Blood circulation. It is notable that Si Wu Tang, which consists of Chuanxiong, Danggui, Baishao and Shudihuang, is a classic recipe of TCM prescriptions for invigorating blood, the blood tonic and the treatment of menstrual irregularities, and has been recognized as the "Preferred Prescription of Gynecology" by succeeding generations of TCM medical practitioners. More

importantly, Baizhu is traditionally recognized in TCM for its effect on the calming fetus and Xiangfu is regarded as the "Sacred Medicine of Gynecology" in TCM. This explains to some extent in the aforementioned results of the data mining, that Xiangfu has been frequently prescribed by combinations with Danggui, Chuanxiong, Baishao, Shudihuang, Baizhu and Gancao in the TCM system.

The results of the cluster analysis presented in Fig. 4 indicated that CMs with the same medicinal properties are more likely to cluster into one class, which is consistent with the above association rule results.

In conclusion, CyRh, in TCM, is traditionally used for treating diseases concerning the digestive system, gynecology and nervous system such as stomach pain, abdominal pain, depression,

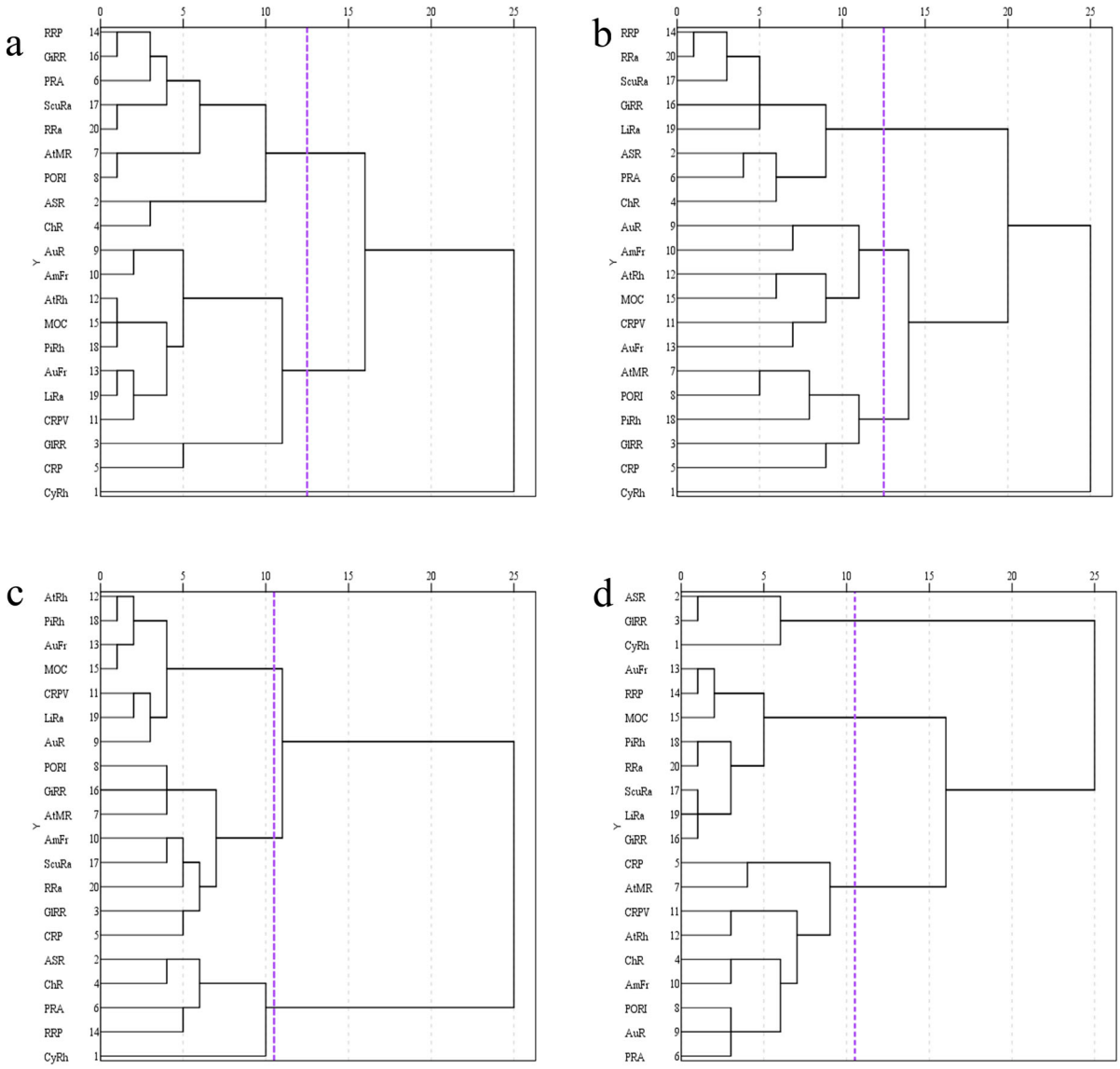


Fig. 4 Hierarchical cluster analysis of the CMs in TCM prescriptions containing CyRh. **a** Hierarchical cluster analysis of the CMs with high-frequencies; **b** Hierarchical cluster analysis of the CMs prescribed for the Spleen system diseases; **c** Hierarchical cluster analysis for the CMs prescribed for the women's menstrual, leucorrhea and miscellaneous diseases; **d** Hierarchical cluster analysis for the CMs prescribed for the fetuses, parturients and their diseases

amenorrhea, dysmenorrhea, menoxenia as well as breast tenderness. The plant which is called "the general medicine to treat Qi disease, and the chief medicine to treat women's diseases", exactly corresponds to the results of the data mining described above. Referring to two important and authoritative criterions, (I) the Chinese national standard 'Clinic terminology of traditional Chinese medical diagnosis and treatment-Diseases' (GB/T 1675.1–1997) and (II) International Classification of Diseases (ICD-10), modern pharmacological studies related to traditional applications of TCM were systematically summarized, as detailed in Table 3. Anti-cervical cancer (Mannarreddy et al. 2017; Saad et al. 2018; Susianti et al. 2018; Lin et al. 2019), anti-breast cancer (Park et al. 2014; Mannarreddy et al. 2017; Simorangkir et al. 2019; Wang et al. 2019; Ma et al. 2020; Samra et al. 2020), anti-ovarian cancer (Ahn et al. 2015; Ryu et al. 2015), anti-depressant activity (Pal et al. 2009; Jia and Zou 2014; Lin et al. 2015; Zhou et al. 2016a, 2016b; Hao et al. 2017), neuroprotective activity (Dabaghian et al. 2015; Sutalangka and Wattanathorn 2017), hepatoprotective activity (Mohamed 2015; Parvez et al. 2019), against gastric mucosal damage (Thomas et al. 2015), anti-gastrointestinal tumors (Al-Shammari et al. 2021) and other effects of CyRh have been well evaluated in modern pharmacological studies. Moreover, CyRh is also used for the treatment of digestive and gynecological disorders including amenorrhea and dysmenorrhea in traditional Indian, Tunisian, and South Korean medicinal systems. All the above are to some extent unified.

Phytochemistry

Due to its wide distribution worldwide, the phytoconstituents of *C. rotundus* have been extensively detected and isolated in many countries over the past decades. The complexity and structural diversity of the chemical composition of this aromatic herb has contributed to its wide-ranging pharmacological activities and medicinal values. Numerous studies have demonstrated that the main component of *C. rotundus* is the volatile oil, which is also the major pharmacologically active ingredient, consisting of a variety of monoterpenes, sesquiterpenes and their oxides. In addition, some flavonoids, saponins, alkaloids, phenylpropanoids, quinonoids, diterpenoids, carbohydrates, aliphatic compounds and several trace elements have also been found to be existent in this plant. Figure 5 and Table 4 distinctly illustrate the multiplicity of chemical constituents of *C. rotundus*. In this part, a total of 552 compounds from *C. rotundus* have been summarized, with 350 and 202 compounds isolated or characterized, respectively. Their detailed chemical information including the name, formula, molecular weight and the originated plant parts are summarized in supplementary Tables S10–17, and their chemical structures are presented in supplementary Fig. S1–23.

Monoterpenoids

The simple monoterpenes and their oxygenated derivatives are an indispensable part of the essential oil of *C. rotundus* (EOCR) and are mainly composed of menthane-type (supplementary Fig. S1) and pinane-type (supplementary Fig. S2) monoterpenoids. Investigation of the available literature indicated that the monoterpenoids isolated from this aromatic herb are predominantly iridoid glycosides, with chemical structures shown in supplementary Fig. S3. Using despair mice models, three iridoid glycosides [rotunduside F (**60**), rotunduside G (**55**) and rotunduside H (**56**)] were shown to exhibit noticeable antidepressant activity by the forced swim test (FST) and the tail suspension test (TST), equivalent to the positive control fluoxetine (Zhou and Fu 2013; Lin et al. 2015; Zhou et al. 2016a). 10-*O*-*p*-Hydroxybenzoylviridoside (**53**), rotunduside **B** (**51**), rotunduside C (**67**) and senburiside I (**66**) displayed macrophages respiratory burst (MRB) inhibitory activity to some extent (Zhou et al. 2013; Zhou and Zhang 2013; Cheng et al. 2014; Zhang et al. 2014).

Sesquiterpenoids

Sesquiterpenoids are the most dominant active constituents in EOCR. To date, there are approximately 260 sesquiterpenoids that have been isolated and characterized from *C. rotundus*, mainly consisting of sesquiterpenes and their oxygenated derivatives such as alcohols, ketones and lactones. Notably, most of them were identified to be separated from the rhizomes or tubers of this plant. The predominant sesquiterpenoid skeletons include eudesmane-type (supplementary Fig. S5), patchoulane-type (supplementary

Table 3 Modern pharmacological studies related to the traditional use of *C. rotundus* in TCM

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Estrogen-like effect	In vivo	Female C57bl/6 mice	By recovering the levels of dopamine in the striatum and behavior performance in MPTP mice and the TH immunopositive fibers and cells	Petroleum ether extract (50 mg/kg/day)	II	3	Rhizomes	Kim et al. (2013)
Anti-estrogenic effect	In vivo	Female Swiss albino mice	Reduction of the thickness in the endometrial layers of the uterine wall	Methanol extract (3375 mg/kg)	II	3	Tubers	Hendri et al. (2016)
Enhance endometrial receptivity	In vivo and in vitro	C57BL/6 female mice; Choriocarcinoma JAr cells and endometrial Ishikawa cells	Increase the expression of LIF and enhance adhesion of JAr cells onto Ishikawa cells to improve the number of implantation sites in pregnant mice	Water extract (31.68 mg/kg/day)	II	3	Tubers	Choi et al. (2017)
Anti-uterine fibroids	In vivo	Female sprague dawley rats	By increasing Bax protein expression and reducing Bcl-2 expression from homodimers Bax/Bax, and decreasing plasma estradiol and progesterone	Amentoflavone (15, 10 and 5 g/kg)	II	3	Rhizomes	Ying and Bing (2016)
Lactogenic activity	In vivo	Lactating dams	By increasing the weight and the protein, carbohydrate content of mammary gland tissue, and stimulating the synthesis of prolactin significantly to increase the milk production	Water extract (300 and 600 mg/kg)	III	3	Rhizomes	Badgujar and Bandivdekar (2015)
Inhibition to fetal growth	In vivo	Female sprague dawley rats	Exhibit inhibitory effects against fetal growth of rats during pregnancy	96% Alcohol extract (22.5, 45, 90 mg/kg)	III	3	Tubers	Hendri et al. (2019); Busman et al. (2020)
Regulation of Integrin $\beta 3$	In vivo	Mice (*Mus musculus* L.)	Reduce the levels of $\beta 3$ integrin of uterine mice during the embryo implantation period	Essential oil	III	3	Tubers	Yulianty and Sutyarso (2019)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Anti-depressant activity	In vivo	Adult swiss albino mice	By enhancing sleeping time and analgesic, reducing different behavioral reflexes, increasing the brain serotonin and GABA levels in mice by anticonvulsant activity	Ethanol extract (40, 60 and 80 mg/kg)	IV	2	Roots and rhizomes	Pal et al. (2009)
Anti-depressant effect	In vivo	Male NIH mice	/	Rotunduside D, rotunduside E, rotunduside F (50 mg/kg)	IV	2	Rhizomes	Lin et al. (2015)
Anti-depressant effect	In vivo	Male NIH mice	/	Rotunduside G, rotunduside H (50 mg/kg)	IV	2	Rhizomes	Zhou et al. (2016a)
Anti-depressant effect	In vivo	Male NIH mice	/	Cyprotuside A and Cyprotuside B (50 mg/kg)	IV	2	Rhizomes	Zhou et al. (2016b)
Antidepressant effect	In vivo	Mice	Reduction of the immobility time in the TST and FST	Ethanol extract	IV	2	Roots	Jia and Zou (2014)
Antidepressant effect	In vivo	Wistar rats	Inhibition of brain MAO activity in rats	Water extract (200, 400 and 800 mg/kg)	IV	2	Whole plant	Hao et al. (2017)
Potential neuroprotective effects	In vivo	Adult male Wistar rats	Amelioration of the CA1 pyramidal cell loss due to transient global ischemia/reperfusion injury	Ethanol extract (100 mg/kg/day)	IV	2	Rhizomes	Dabaghian et al. (2015)
Neuroprotective and cognitive-enhancing effects	In vivo	Male Wistar rats	Enhance memory, increase neuronal density, decrease AChE activity, decrease oxidative stress status and activate pERK1/2 CP1-treated in rats	95% Ethanol extract (100, 200 and 300 mg/kg)	IV	2	Aerial part	Sutalangka and Wattanathorn (2017)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Potential against Alzheimer's disease	In vivo	Male Wistar rats	Improvement of spatial learning and memory in rats might be related to the mediation of the cholinergic nervous system and exhibit potent antioxidant activity by regulating the enzyme levels such as SOD, CAT, GPx and GR in brain tissue	Ethanol extract (100 and 200 mg/kg)	IV	2	Tubers	Rabiei et al. (2013)
Potential against Alzheimer's disease	In vivo	Wistar male rats	The increase of escape latency and traveled distance, improvement of the learning impairment and improvement of AD-induced cognitive dysfunction	80% Ethanol extract (400 mg/kg)	IV	2	Powder	Mehdizadeh et al. (2017)
Potential against Alzheimer's disease	In vivo	Male Wistar rats	The increase of spatial memory, neuronal differentiation in the hippocampus	Chloroform fraction (250, 500, and 750 mg/kg)	IV	2	Rhizomes	Shakerin et al. (2020)
Against Hypoxia injury	In vivo	Inbred male Wistar rats	The protection against the cognitive impairments, muscular coordination defects and the locomotor activity	Ethanol extract (200 and 400 mg/kg)	IV	2	Tubers	Jebasingh et al. (2014)
Against Hypobaric hypoxia	In vivo	Sprague–Dawley rats	Amelioration of hypobaric hypoxia-induced memory impairment and neurodegeneration in the hippocampus through its anti-stress effects	TOF Extract (150, 300 and 600 mg/kg)	IV	2	Roots	Kandikattu et al. (2017)
Against neurotoxicity	In vivo	Albino Wistar rats	Protective effect against esfenvalerate by ameliorating levels of antioxidant enzymes, acetylcholine esterase, and inflammatory markers	Methanol extract (100 mg/kg)	IV	2	Tubers	Hussein et al. (2020)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Hepatoprotective activity	In vivo	Wister rats	Anti-hepatotoxic, anti-hepatitis B virus and modulation of hepatic CYP450	80% Ethanol extract (IC_{50}: 100 μg/mL)	V	1	Rhizomes	Parvez et al. (2019)
Hepatoprotective activity	In vivo	Adult male albino rats	By improving the activity of SGOT, SGPT, and total bilirubin, scavenging free radicals for the lipoperoxidants, reactive oxygen species (ROS) and NO and maintaining the liver antioxidative defense systems	EtOAc fraction (100 mg/kg)	V	1	Rhizomes	Mohamed (2015)
Against non-alcoholic fatty liver disease	In vivo	Male C57BL/6 mice	Reduction of the expression levels of hepatic lipogenic genes	The hexane fraction	V	1	Rhizomes	Oh et al. (2015)
Cytoprotective effects against gastric ulceration	In vivo	Female Sprague–Dawley rats	Effects on protecting the stomach, delay gastric motility, and delayed gastric emptying of resin pellets	Water extract (1250, 2500, 4000 mg/kg)	I	1	Rhizomes	Zhu et al. (1997)
Against gastric mucosal damage	In vivo	Male Wistar rats	By inhibiting oxidative stress, increasing the activity of SOD, cellular glutathione and GSH-Px and inhibiting the lipid peroxidation in the gastric mucosa of ulcerated animals	70% Methanol extract (250 and 500 mg/kg)	I	1	Rhizomes	Thomas et al. (2015)
Potential anti-cervical cancer	In vitro	Cervical cancer (HeLa) cells and human glioblastoma (AMGM) cells	Reduction of the expression levels of OCT3/4, MMP2 and MMP9	TOF Extraction (50–500 μg/mL, the best concentration of inhibition: 350 μg/mL)	II	3	Tubers	Saad et al. (2018)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Potential anti-cervical cancer	In vitro	HeLa cervical cancer cells	/	The hydrodistilled essential oil (IC_{50}: 35.062 ± 11.258 μg/mL)	II	3	Tubers	Susianti et al. (2018)
Potential anti-cervical cancer	In vitro	HeLa human cervical cancer cells	Induction of gene expression which is associated with apoptosis and cell-cycle arrest	Ethanol extract (IC_{50}: 300 μg/mL)	II	3	Rhizomes	Lin et al. (2019)
Potential anti-cervical cancer	In vitro	HeLa cervical cancer cells	/	Methanol extract (IC_{50}: 6.83 ± 0.79 μg/mL)	II	3	Rhizomes	Mannarreddy et al. (2017)
Potential anti-breast carcinoma	In vitro	Breast carcinoma (MCF-7) cells	/	The hydrodistilled essential oil (IC_{50}: 170.8 ± 0.567 μg/mL)	II	3	Rhizomes	Samra et al. (2020)
Potential anti-triple-negative breast cancer	In vitro	TNBC cells lines (MDA-MB-468 and MDA-MB-231)	Induction of apoptosis by arresting the pathways of carbohydrate metabolism and nucleotide sugar metabolism and impacting the energy metabolism of TNBC cells	95% Ethanol extract (MDA-MB-468: IC_{50}: 773.3 μg/mL; MDA-MB-231: IC_{50}: 537.5 μg/mL)	II	3	Rhizomes	Ma et al. (2020)
Potential anti-triple-negative breast cancer	In vitro	TNBC cells lines (MDA-MB-468 and MDA-MB-231)	By arresting cell cycle in G_0/G_1 phase induces apoptosis by promoting the expression of BAX and inhibiting the expression of BCL-2 3-MA	95% Ethanol extract (0, 200, 400, 600, 800, 1000 and 1200 μg/mL)	II	3	Rhizomes	Wang et al. (2019)
Potential anti-breast cancer	In vitro	Breast carcinoma (MCF-7) cells	/	Methanol extract (IC_{50}: 4.52 ± 0.57 μg/mL)	II	3	Rhizomes	Mannarreddy et al. (2017)
Potential anti-breast cancer	In vitro	MCF-7 cell and Vero cells	By arresting the cell cycle in the G_0-G_1 phase and inducing apoptosis	*n*-Hexane fraction (IC_{50}: 120.819 μg/mL)	II	3	Rhizomes	Simorangkir et al. (2019)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Potential anti-breast cancer	In vitro	MDA-MB-231 human breast carcinoma cells	Activation of both intrinsic and extrinsic signaling pathways to regulate the caspase-dependent cascade	Ethanol extract Methanol extract (0–500 μg/mL)	II	3	Rhizomes	Park et al. (2014)
Potential anti-ovarian cancer	In vitro	Human ovarian cancer cells (A2780) and endometrial adenocar cinoma (Ishikawa)	/	AcOEt fraction (IC_{50}: 74.60 and 177.61 μg/mL) 11,12-Dihydroxyeudesm-4-en-3-one (IC_{50}: 11.06 ± 0.25 and 6.46 ± 0.12 μM)	II	3	Rhizomes	Ryu et al. (2015)
Potential anti-ovarian cancer	In vitro	Endometrial adenocar cinoma (Ishikawa)	/	Cyperusol A3 (86.85 ± 0.41 μM)	II	3	Rhizomes	Ryu et al. (2015)
Potential anti-ovarian cancer	In vitro	Ovarian cancer cell lines (A2780, SKOV3 and OVCAR-3)	By inducing caspase-dependent apoptosis in human ovarian cancer cells	*n*-Hexane fraction (IC_{50}: 50.48 ± 1.07, 87.34 ± 0.56 and 149.04 ± 0.87 μg/mL) EtOAc fraction (IC_{50}: 74.60 ± 0.52, 80.72 ± 1.92 and 134.75 ± 0.98 μg/mL) 80% EtOH extract (A2780: IC_{50}: 135.33 ± 0.14 μg/mL)	II	3	Rhizomes	Ahn et al. (2015)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Potential anti-ovarian cancer	In vitro	Ovarian cancer cell lines (A2780, SKOV3 and OVCAR-3)	By inducing caspase-dependent apoptosis in human ovarian cancer cells	6,9-Diacetoxy cyperene (IC_{50}: 89.75 ± 1.27, 118.63 ± 0.01, 114.45 ± 0.12 μg/mL) 6-Acetoxy Cyperene (IC_{50}: 61.69 ± 2.25, 89.17 ± 0.06, 100.42 ± 0.02 μg/mL)	II	3	Rhizomes	Ahn et al. (2015)
Potential anti-ovarian cancer	In vitro	Endometrial cancer (Hec1A and Ishikawa) cells	By inducing caspase-dependent apoptosis in human ovarian cancer cells	*n*-Hexane fraction (110.62 ± 0.37 and 164.07 ± 0.23 μg/mL) EtOAc Fraction (IC_{50}: 131.43 ± 0.95 and 177.61 ± 0.53 μg/mL)	II	3	Rhizomes	Ahn et al. (2015)
Estrogen-like effect	In vitro	MCF-7 BUS cells	By increasing transcriptional activity in estrogen-sensitive gene	4α,5α-Oxidoeudesm-11-en-3-one (3.75–60 μg/mL)	II	3	Rhizomes	Park et al. (2019)
Potential anti-endometrial adenocarcinoma cancer	In vitro	Human endometrial adenocarcinoma cells (Ishikawa)	/	AcOEt fraction (IC_{50}: 177.61 μg/mL)	II	3	Rhizomes	Ryu et al. (2015)
Neuroprotective effects	In vitro	The human neuroblastoma cell line (SH-SY5Y)	Amelioration of the H_2O_2-induced oxidative stress by improving the antioxidant status, mitochondrial membrane integrity, regulating the apoptotic markers and maintaining the BDNF level	Water extract (0, 1, 10, 25, 50, and 100 μg/mL)	IV	2	Roots	Kumar and Khanum (2013)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Against neuronal damage	In vitro	PC12 cells	Inhibition of the generation of reactive oxygen species and nitric oxide, reduction of mitochondrial membrane potential, and caspase-3 activity induced by 6-OHDA, protective effect against damage to dopaminergic neurons	Water extract (50 and 100 μg/mL)	IV	2	Rhizomes	Lee et al. (2010)
Potential anti-hepatocellular carcinoma cancer	In vitro	Hepatocellular carcinoma (HepG2) cells	/	The hydrodistilled essential oil (IC_{50}: 204.1 ± 1.25 μg/mL)	V	1	Rhizomes	Samra et al. (2020)
Potential anti-liver cancer	In vitro	Hepatocellular carcinoma (HepG2) cells	/	Methanol extracts (IC_{50}: 7.66 ± 0.82 μg/mL)	V	1	Rhizomes	Mannarreddy et al. (2017)
Hepatoprotective activity	In vitro	Hepatocellular carcinoma (HepG2) cells	Anti-hepatotoxic, anti-hepatitis B virus and modulation of hepatic CYP450	Ethyl acetate, *n*-butanol and aqueous fractions (IC_{50}: 64.24, 94.86, 107.81 μg/mL)	V	1	Rhizomes	Parvez et al. (2019)
Anti-hepatitis B virus	In vitro	HepG2.2.15 cells (HBsAg and HBeAg Elisa)	/	Ethyl acetate, aqueous, *n*-butanol extracts (IC_{50}: 64.24, 94.86, 107.81 μg/mL)	V	1	Rhizomes	Parvez et al. (2019)
Anti-infectious diarrhea	In vitro	*E. coli* B170, *E. coli* E134, *E. coli* B831-2, *Vibrio cholerae* C6709 and *Shigella flexneri* M9OT	By reducing bacterial adherence and regulating the production of CT and action of LT, directly killing the pathogen to exerts its antidiarrheal action	Water extract (0.52 ± 0.028, 2.6 ± 0.14 and 5.2 ± 0.28 mg/mL)	I	1	Tubers	Daswani et al. (2011)

Table 3 continued

Effect	Type of study	Species/enzymes	Mechanism/effect	Extract/compound (Dose/IC_{50})	Corresponding TCM indications[a]	International Classification of diseases[b]	Part of plant	References
Therapy for gastrointestinal tumors	In vitro	Esophagus cancer, hepatocellular carcinoma, human rectal cancer	The combination therapy of NDV-alkaloid extract had synergistic and enhanced anticancer activity, with upregulating *p*53 level	Alkaloid extract (100 μg/mL)	I	1	Rhizomes	Al-Shammari et al. (2021)

[a] I, The Spleen system; II, Women's menstrual, leucorrhea and miscellaneous diseases; III, Fetuses, parturients and their diseases; IV, The Brain system; V, The Liver system; [b] 1, The digestive system diseases; 2, The nervous system diseases; 3, The gynecological diseases

Fig. S6), and cadinane-type (supplementary Fig. S7) sesquiterpenoids. A summary of the sesquiterpenoid skeletons in *C. rotundus* is presented in Fig. 6.

It is worth pointing out that several of the published pharmacological effects of *C. rotundus* may be attributed to the most abundant and major bioactive components of eudesmane-type, patchoulane-type, eremophilane-type (supplementary Fig. S10) sesquiterpenoids, such as α-cyperone (**111**), isocyperol (**96**), nootkatone (**235**) and valencene (**237**). Khan et al. pointed out that α-cyperone (**111**), isocyperol (**96**) and nootkatone (**235**), valencene (**237**), *β*-selinene (**97**) expressed a powerful anti-inflammatory effect on LPS-stimulated RAW 264.7 cells (Khan et al. 2011; Seo et al. 2014). There are also several research works showing convincingly that nootkatone (**235**) and valencene (**237**) exerted anti-allergic activity either in vitro or in vivo and increased the survival rates in septic mice on account of heme oxygenase-1 induction (Jin et al. 2011; Tsoyi et al. 2011). Besides, nootkatone (**235**) exerted potent DPPH radical scavenging capacity, with IC_{50} valued 22.03 μM, followed by aristolone (**296**) and solavetivone (**302**), with IC_{50} values of 24.18 and 31.24 μM, respectively (Priya Rani and Padmakumari 2012). Some sesquiterpenoids isolated from *Cyperus rotundus* tubers were found to possess varying degrees of antimalarial effects against *Plasmodium falciparum*, as exemplified by patchoulenone (**152**, EC_{50}: 0.108 M), caryophyllene α-oxide (**241**, EC_{50}: 0.345 μM), 10,12-peroxycalamenene (**318**, EC_{50}: 2.33×10^{-3} μM), α-cyperone (**111**, EC_{50}: 25 μM) and *β*-selinene (**97**, EC_{50}: 27 μM) (Weenen et al. 1990a; Thebtaranonth et al. 1995). In addition, 11,12-dihydroxyeudesm-4-en-3-one (**110**, EC_{50}: 11.06 ± 0.25 μM) showed a more potent proliferation inhibitory effect against ovarian cancer A2780 cells than 6,9-diacetoxy cyperene (**143**, EC_{50}: 61.69 ± 2.25 μM). Again, 11,12-dihydroxyeudesm-4-en-3-one (**110**, EC_{50}: 6.46 ± 0.12 μM) and cyperusol A3 (**197**, EC_{50}: 86.54 ± 0.41 μM) also exhibited detectable cytotoxicities against endometrial adenocarcinoma *Ishikawa* cells (Ahn et al. 2015; Ryu et al. 2015). There was an interesting discovery that 4α,5α-oxidoeudesm-11-en-3-one (**105**) exerts a dual regulation on estrogen receptor-α and estrogen receptor-*β* and possesses both estrogenic and antiestrogenic effects depending on the E2 concentration (Park et al. 2019).

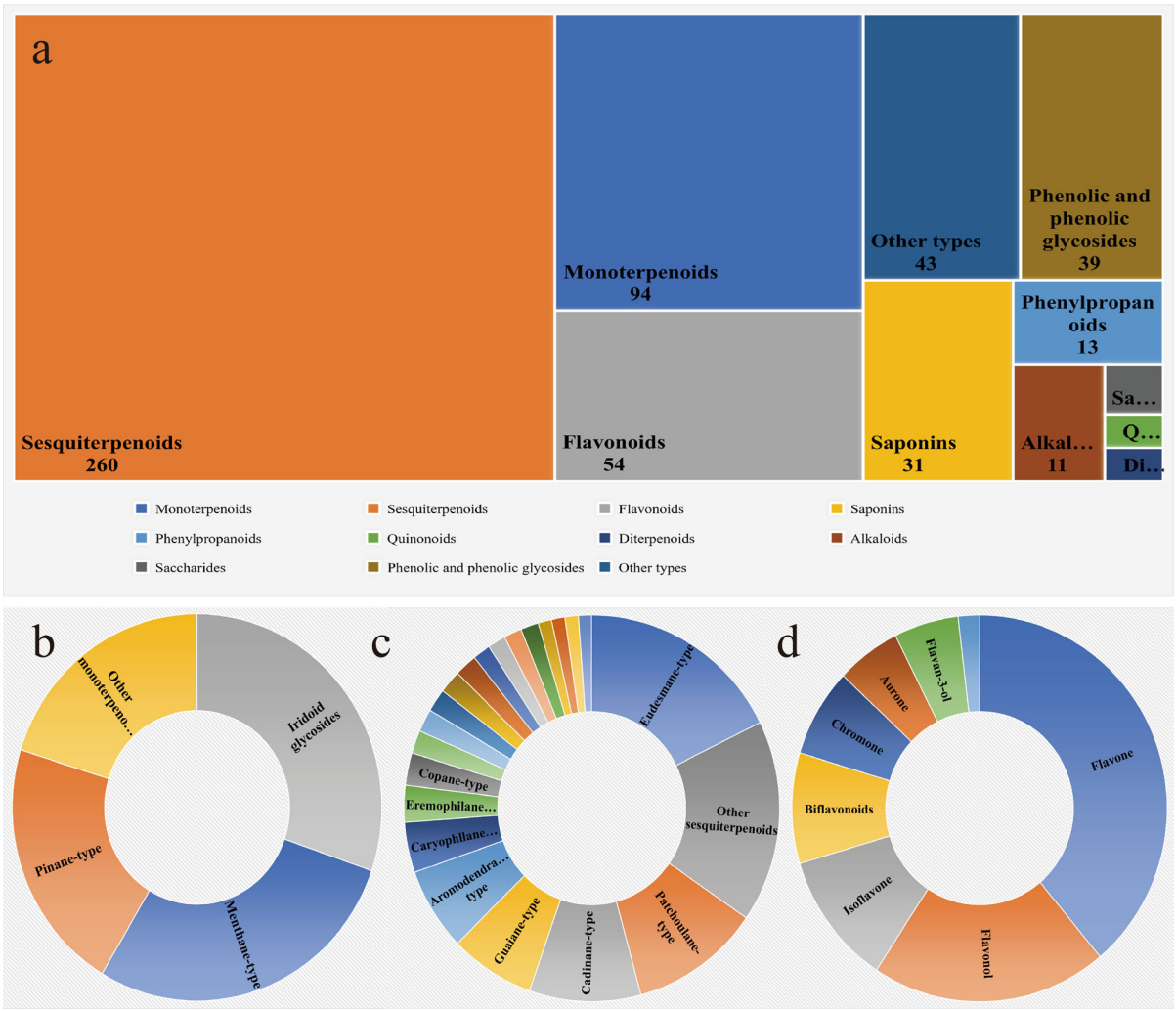


Fig. 5 Distribution of chemical constituents of *C. rotundus*. **a** Treemap showing the constituent distribution by roughly compound type from *C. rotundus*; **b** Distribution of the sub-type of monoterpenoids; **c** Distribution of the sub-type of sesquiterpenoids; **d** Distribution of the sub-type of flavonoids

Additionally, a norsesquiterpenoid norcyperone (**343**) and a sesquiterpenoid cyperensol A (**344**) characterized with a unique 6/6/5 skeleton, have been isolated and identified from the rhizomes of *C. rotundus* (Xu et al. 2008; Wang et al. 2021b). Again, three novel sesquiterpenoid alkaloids (supplementary Fig. S13) rotundines A–C (**352–354**) have been reported by Jeong et al. (Jeong et al. 2000) to be isolated from the methanol extract of the rhizomes of *C. rotundus*.

Flavonoids

Flavonoids are extensively distributed in the plant kingdom with a wide variety of biological activities, which have attracted worldwide attention (Bai et al. 2019). Flavonoids are mainly found in the rhizomes and aerial parts such as the leaves of *C. rotundus* (Sayed et al. 2007, 2008; Ibrahim et al. 2018). Until now, a total of fifty-four flavonoids have been isolated and identified from *C. rotundus*, with chemical structures as displayed in the supplementary Fig. S14–18. Flavone-type and flavonol-type are the predominant types of flavonoids isolated from *C.*

Table 4 Summary of the chemical constituents in *C. rotundus*

Type	Number of compounds
Monoterpenoids	94
Sesquiterpenoids	260
Flavonoids	54
Saponins	31
Phenylpropanoids	15
Quinonoids	2
Diterpenoids	2
Alkaloids	11
Saccharides	3
Phenolic and phenolic glycosides	37
Other types	43
Total	552

rotundus. Besides these, the isoflavone-type, biflavonoids and other types of flavonoids have also been discovered to be present in *C. rotundus*. Among them, four biflavone constituents namely amentoflavone (**393**), ginkgetin (**394**), isoginkgetin (**395**) and sciadopitysin (**396**), were obtained from the ethanol extract of rhizomes of *C. rotundus*. And amentoflavone showed a significant effect on anti-uterine fibroids in pathological rat models (Ying and Bing 2016). 7,8-Dihydroxy-5,6-methylenedioxyflavone (**362**) was isolated from the rhizomes of *C. rotundus* (Zhou and Fu 2013); while vitexin (**365**), isovitexin (**366**), orientin (**367**), epiorientin (**368**), luteolin 4′-*O*-*β*-D-glucuronopyranoside (**370**), luteolin 7-*O*-*β*-D-glucuronopyranoside (**371**), cyperaflavoside (**375**), myricetin 3-*O*-*β*-D-galactopyranoside (**382**), quercetin 3-*O*-*β*-D-glucopyranoside (**383**), and myrcetin 3-*O*-*β*-D-

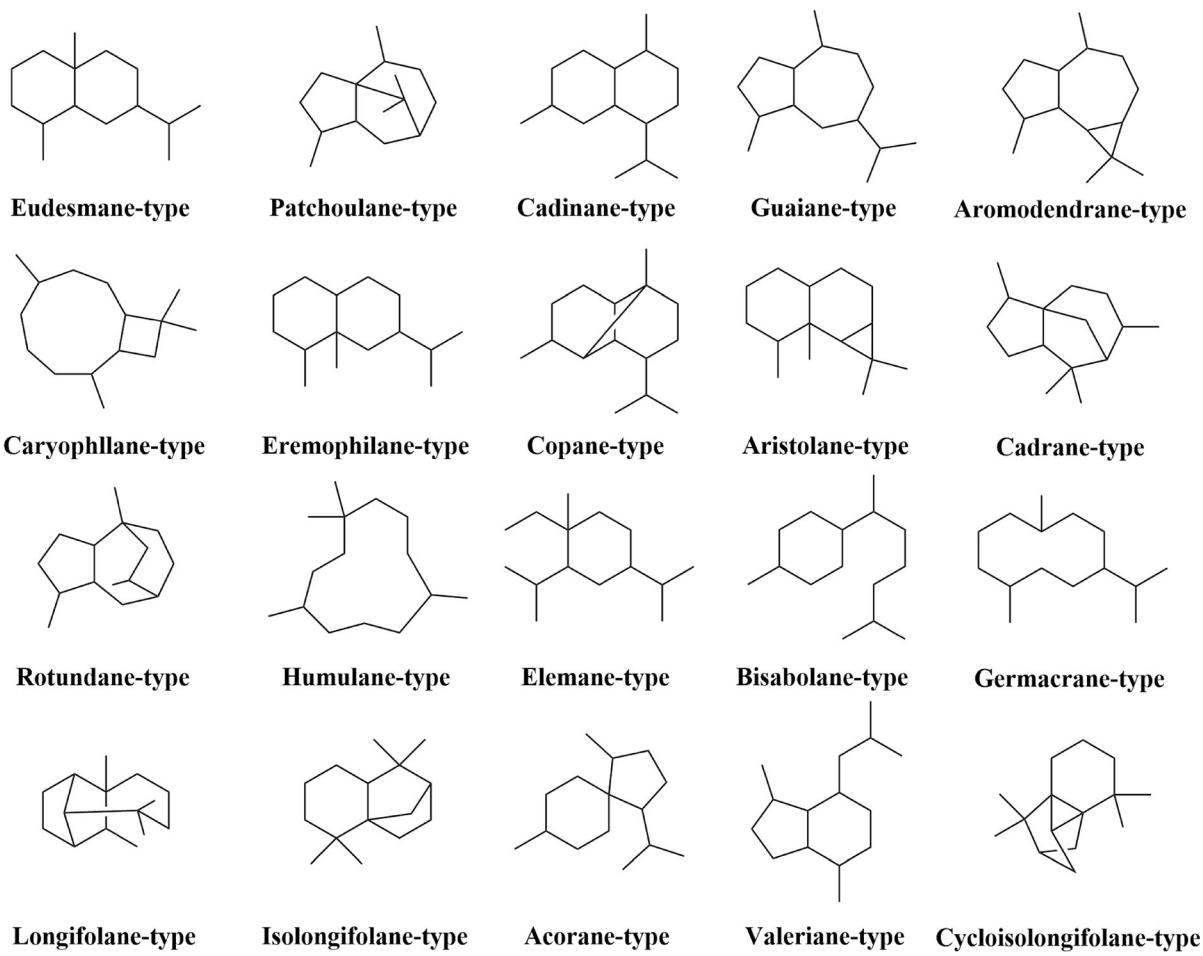


Fig. 6 Basic sesquiterpenoid skeletons in *C. rotundus*

glucopyranoside (**384**) were given from the aerial parts of *C. rotundus* (Sayed et al. 2008; Ibrahim et al. 2018). Compounds **365–368**, **370–371** and **382** exhibited significant antioxidant activities (Sayed et al. 2008), and compounds **365**, **367**, **371**, **375**, **383**, and **384** possessed significant 5-lipoxygenase inhibitory activity with IC_{50} values at 5.1, 4.5, 5.9, 4.0, 3.7, and 2.3 μM, respectively (Ibrahim et al. 2018). As is reported, khellin (**403**) and visnagin (**404**) were reported to show strong cytotoxic activities against L5178y (mouse lymphoma cells) with ED_{50} of 4.5 and 0.9 μg/mL, respectively, and also inhibit significantly the growth of the neonate larvae of the pest insect *Spodoptera littoralis* to exert the antifeedant activity (Sayed et al. 2007).

Triterpenoids and steroids

Saponins in *C. rotundus* are of considerable importance in the treatment of inflammation as well as depression. Supplementary Fig. S19 displays a summary of the structures of thirty-one triterpenoids and steroids discovered in *C. rotundus*. Among them, the cycloartane glycosides cyprotuside A **(435),** cyprotuoside B **(436)**, cyprotuoside C **(433)**, cyprotuoside D **(434)**, which were isolated from the 95% aqueous ethanol extract of the rhizome of *C. rotundus* (Yang and Shi 2012; Zhou et al. 2016b; Lin et al. 2018), with a 9,10-*seco*-cycloartane framework that has seldom been reported from a natural source. Cyprotuoside A **(435)** and cyprotuoside B **(436)** showed remarkable antidepressant activity in the despair mice models (Zhou and Zhang 2013). Furthermore, a classic lupine-type triterpenoid lupeol **(420)**, to a certain extent, expressed anti-inflammatory activity and IL-1β inhibitory activity in THP-1 monocytic cells.

Phenylpropanoids

So far, a total of 15 phenylpropanoids have been isolated or characterized from *C. rotundus*. They generally consist of simple phenylpropanoids (**440–451**), coumarins (**452–453**) and lignans (**454**), as listed in supplementary Fig. S20. Among them, *p*-coumaric acid (**443**), caffeic acid (**445**), (-)-(*E*)-caffeoylmalic acid (**447**) and chlorogenic acid (**446**) exhibited significant antioxidant activities (Sayed et al. 2008).

Phenolic compounds and phenolic glycosides

Phenolic compounds are largely composed of phenylpropanoids, flavonoids, and some other phenolic acid components. As phenylpropanoids and flavonoids have been detailed in the preceding sections, this section focused on some other phenolics or phenolic glycosides as shown in supplementary Fig. S22. For example, scirpusins A–B (**494–495**) (Sim et al. 2016) which were obtained from the 80% EtOH extract of *C. rotundus* rhizomes using bioactivity-guided fractionation, remarkably provided in vitro protection against neurotoxins for neuronal cells. In addition, five natural α-glucosidase inhibitors, cyperusphenol A (**497**), mesocyperusphenol A (**499**), cyperusphenol D (**493**), scirpusins A (**494**) and scirpusins B (**495**) have been successfully fished out (Cao and Ou 2015) from the *C. rotundus* extracts using immobilized enzyme technique in combination with UHPLC-QTOF MS analysis.

Other compounds

Apart from the aforementioned, diterpenoids (**455–456**), quinonoids (**457–458**), nitrogenous compounds (**459–469**), carbohydrates (**470–472**) and some other compounds (**510–552**) were also detected to be present in *C. rotundus*, as shown in supplementary Fig. S21–S23. Among them, fulgidic acid (**532**) could suppress LPS-induced iNOS, COX-2, TNF-α, and IL-6 expression effectively by activator protein-1 (AP-1)AP-1 inactivation in RAW264.7 macrophages to exert its anti-inflammatory activity (Shin et al. 2015).

Separation, identification and analytical methods

Separation techniques

Presently, various separation techniques have been employed for the isolation and purification of chemical components of *C. rotundus*. Among them, the conventional separation procedures include silica gel column chromatography, sephadex LH-20 column chromatography, alumina column chromatography, reversed-phase (ODS, RP-18, MCI, YMC) column chromatography, macro porous absorption resin (Diaion HP-20) column chromatography, thin-layer chromatography (TLC), preparative thin-layer chromatography

(PTLC), HPLC with C18 column, semi-preparative HPLC and preparative HPLC (PHPLC) (Morimoto and Komai 2005; Kim et al. 2012; Cheng et al. 2014; Zhang et al. 2014; Shin et al. 2015; Xu et al. 2015; Liu et al. 2016).

Moreover, several alternative techniques have been applied in the purification of the secondary metabolites of *C. rotundus*. MPLC (RediSep SiO_2) and MPLC (RediSep C_{18}) were employed to obtain two novel sesquiterpenoids and three identified ones by Ryu et al. (Ryu et al. 2015). Park et al. purified six sesquiterpenoids from the methanolic extract of *C. rotundus* (MECR) rhizomes based on estrogenic activity, obtained by a combination of silica gel column chromatography and cycling HPLC chromatography with JAIGEL-1H and 2H columns (Park et al. 2019). A flash chromatographic system equipped with a C18 flash column was adopted to conduct the separation of fulgidic acid (**532**) (Shin et al. 2015). Supercritical fluid extraction (SFE) and high-speed counter-current chromatography (HSCCC) were used for the first time to acquire high-purity α-cyperone (**111**) of much quantities from EOCR (Shi et al. 2009). Xu et al. obtained thirty-seven sesquiterpenoids based on anti-hepatitis B virus activity-oriented isolation by associating common chromatographic separation techniques with ultra-fast liquid chromatography-mass spectrometry (UFLC-MS^n) and HR-MS (Xu et al. 2015). Sonwa and König also for the first time performed the pre-fractionation of EOCR on a silica column coupled with a condenser and successively isolated (-)- isorotundene (**254**) by PTLC on silver nitrate precoated plates (Sonwa and König 2001).

Identification techniques

The structural identification of the isolated phytoconstituents from *C. rotundus* has been performed successfully using recognized chromatographic and spectroscopic techniques such as TLC, IR, UV, EI-MS, HR-ESI–MS, MALDI-TOF MS, FAB-MS, HR-DART-MS, 1D/2D NMR (including ^{1}H NMR, ^{13}C NMR, DEPT, HMBC, HSQC, ^{1}H-^{1}HCOSY, ROESY and NOESY), ECD and X-ray crystallography (Sayed et al. 2008; Liu et al. 2010; Ito et al. 2012; Zhou and Yin 2012; Zhou et al. 2013; Cheng et al. 2014; Lin et al. 2018; Samra et al. 2021). Given the presence of glycosidic compounds in *C. rotundus*, such as rotunduside G (**55**), rotunduside H (**56**), rotunduside A (**68**), sitosteryl-(6′-hentriacontanoyl)-β-D-galactopyranoside (**427**), cyprotuoside C (**433**), cyprotuoside D (**434**)**,** cyprotuside A (**435**) and cyprotuside B (**436**), identification of the structure and especially the absolute configuration of the sugar residues (*viz.* glycones) is typically aided by acid hydrolysis of the analytes followed by GC comparisons with authentic standards. Q-TOF–MS aided by available standards has been carried out for the identification of certain constituents including (*E*)-cyperusphenol A (**497**), mesocyperusphenol A (**499**), cyperusphenol D (**493**), scirpusins A–B (**494**–**495**), and sugetriol (**163**) (Sayed et al. 2007; Zhou and Zhang 2013; Cao and Ou 2015; Zhou et al. 2016a, 2016b; Lin et al. 2018). On the other hand, MS combined with GC is frequently applied for characterizing the volatile components of *C. rotundus* (Lawal and Oyedeji 2009; Ghannadi et al. 2012; Eltayeib and Ismaeel 2014; Richa and Suneet 2014; Aeganathan et al. 2015; Samra et al. 2020; Qu et al. 2021).

Analytical methods

With the purpose of better qualitative and quantitative analysis of *C. rotundus*, numerous techniques including TLC, PTLC, HPTLC, GC, GC–MS, HPLC/UHPLC, UPLC-QTOF-MS, LC–ESI–MS/MS, PIXE and ICP-MS have been employed. Table 5 and supplementary Table S18 summarized in detail the analytical methods of *C. rotundus*, focusing mainly on the analyses of volatile oils, sesquiterpenoids and some phenolic constituents such as solavetivone (**302**), aristolone (**296**)**,** nootkatone (**235**), scirpusins A (**494**), gallic acid (**484**), etc. The majority of the analyses of *C. rotundus* were performed by GC–MS for qualitative and semi-quantitative analysis of the essential oil.

GC analysis

Gas chromatography has been widely implemented for the rapid and efficient detection of volatile or non-volatile compounds not limited to the food industry alone but also in the pharmaceutical field. Gas chromatography-flame ionization detector (GC-FID), gas chromatography–olfactometry-mass spectrometry (GC-O-MS), and gas chromatography-mass spectrometry (GC–MS) were used for the analysis of the volatile constituents of *C. rotundus* (Table 5).

Table 5 GC–MS determination methods for chemical constituents in *C. rotundus*

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
China-Anhui	GC–MS	Essential oils (extracted by hydrodistillation)	0.52%	DB-1MS capillary column (60 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Relative retention indices calculated against *n*-alkanes	Rhizomes	Qu et al. (2021)
Egypt-Bahtim	GC–MS	Essential oils (extracted by hydrodistillation)	0.40%	DB-5 MS column (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	Kovats' retention index relative to *n*-alkanes (C_8–C_{22})	Rhizomes	Samra et al. (2020)
Iran-Khuzestan-Ahvaz	GC–MS	Essential oils (extracted by hydrodistillation)	/	TRACE-TR-5 capillary column (30 m × 0.53 mm × 0.25 μm)	Helium	Gradient	Kovats' retention indices calculated against aliphatic hydrocarbons (C_5–C_{20})	Rhizomes	Janaki et al. (2018)
China-Shandong	GC–MS	Essential oils (extracted by hydrodistillation)	0.83%	HP-5 MS capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention Indices calculated against a homologous series of *n*-alkanes (C_8–C_{24})	Rhizomes	Hu et al. (2017); Zhang et al. (2017)
Sudan-West Kordofan	GC–MS	Essential oils (extracted by hydrodistillation)	2.60%	Rtx-5 MS capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention index (RI) relative to *n*-alkanes (C_{10}–C_{24})	Rhizomes	Yagi et al. 2016)
China-Hainan	GC–MS	Essential oils (extracted by hydrodistillation)	/	OV-I (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Relative retention index calculated against *n*-alkanes (C_8–C_{20})	Rhizomes	He et al. (2015)

Table 5 continued

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
India-New Delhi	GC–MS	Essential oils (extracted by hydrodistillation)	/	Omegawax^{TM} 250 Flused silica capillary column	Helium	Gradient	/	Rhizomes	Richa and Suneet (2014)
China-Zhejiang	GC–MS	Essential oils (extracted by hydrodistillation)	0.78%	HP-5 MS column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices calculated against a homologous series of *n*-alkanes (C_8–C_{24})	Rhizomes	Liu et al. (2016)
India-Bareilly	GC–MS	Essential oils (extracted by hydrodistillation)	/	DB-1 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention index relative to *n*-alkanes	Rhizome	Gupta et al. (2016)
Sudan-Kordofan-Elrahad	GC–MS	Essential oils (extracted by hydrodistillation)	2.90%	DB-5 MS (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	Kovats retention indices calculated using *n*-alkanes (C_8–C_{20})	Rhizomes	Eltayeib and Ismaeel (2014)
Sudan-Kordofan-Elobeid	GC–MS	Essential oils (extracted by hydrodistillation)	0.60%	DB-5 MS (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	Kovats retention indices calculated using *n*-alkanes (C_8–C_{20})	Rhizomes	Eltayeib and Ismaeel (2014)
Sudan-Kordofan-Bano	GC–MS	Essential oils (extracted by hydrodistillation)	1.80%	DB-5 MS (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	Kovats retention indices calculated using *n*-alkanes (C_8–C_{20})	Rhizomes	Eltayeib and Ismaeel (2014)
China-Shandong	GC–MS	Essential oils (extracted by hydrodistillation)	/	HP-5 quartz capillary column (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Li (2013)
China-Hainan	GC–MS	Essential oils (extracted by hydrodistillation)	/	HP-5 quartz capillary column (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Li (2013)

Table 5 continued

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
Iran-Isfahan	GC–MS	Essential oils (extracted by hydrodistillation)	0.20%	HP-5MS capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices relative to *n*-alkanes	Tubers	Ghannadi et al. (2012)
China-Anhui	GC–MS	Essential oils (extracted by hydrodistillation)	0.40%	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Chen et al. (2011)
Tunisia-Monastir	GC–MS	Essential oils (extracted by hydrodistillation)	0.50%	polar SGE BPX-70 (60 m × 0.25 mm × 0.25 mm) cap. column and apolar Supelco SPB-5 (50 m × 0.25 mm × 0.25 mm) cap. column	Helium	Gradient	Kovats indices calculated from the injection of alkanes (C_7–C_{31})	Tubers	Kilani et al. (2008b)
China-Guangzhou	GC–MS	Essential oils (extracted by hydrodistillation and SFE)	2.4%(SFE)	BP1 quartz capillary column (60 m × 0.22 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Feng et al. (2006)
China-Guangxi	GC–MS	Essential oils (extracted by hydrodistillation)	0.26%–0.97%	HP-5 quartz capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Jin et al. (2006)
China-Guangzhou	GC–MS	Essential oils (extracted with mixed solvent by ultrasonic)	/	DB -1701 quartz capillary column (30 m × 0.35 mm × 1.00 μm)	Helium	Gradient	/	Rhizomes	Lin et al. (2006)
China-Guiyang	GC–MS	Essential oils of CyRh and processed product (extracted by hydrodistillation)	0.82% (raw product), 0.76% (processed product)	HP-5 MS quartz capillary column (30 m × 0.32 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Xu et al. (2006)
Tunisian-Monastir	GC–MS	Essential oils (extracted by hydrodistillation)	0.50%	HP-5 fused silica capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices relative to a series of *n*-alkanes	Tubers	Kilani et al. (2005a)
Egypt-Guiza	GC–MS	Essential oils (extracted by hydrodistillation)	0.46%	Carbowax 20 M coated capillary column (50 m × 0.2 mm × 0.2 μm)	Helium	Gradient	/	Tubers	El-Gohary (2004)
China-Zhejiang	GC–MS	Essential oils (extracted by hydrodistillation)	/	HP-1MS quartz capillary column (50 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Wu (2007)
China-Guangdong	GC–MS	Essential oils (extracted by hydrodistillation)	0.25%–0.41%	HP-5 MS column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Lin et al. (2017)
Iraq	GC–MS	Methanol extracts	/	Capillary column (InertCap 1MS, 30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Tubers	Abo-Altemen et al. (2019)

Table 5 continued

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
India-Mangalore	GC–MS	*n*-hexane extracts	/	Perkin Elmer Elite-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Nidugala et al. (2015)
India-Tamilnadu	GC–MS	Chloroform fraction	/	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Aeganathan et al. (2015)
Hawaii	GC–MS	Essential oils (extracted by *n*-hexane)	/	DB-5 fused silica capillary column (20 m × 0.25 mm)	Helium	Gradient	/	Tubers	Komai and Tang (1989)
India-Tamilnadu	GC–MS	Ethanol extracts (Soxhlet extraction)	/	Elite-5 fused silica capillary column (30 m × 250 μm 1D × 1 μm df)	Helium	Gradient	/	Leaves	Elezabeth and Arumugam (2014)
Brazil	GC–MS	Essential oils (extracted by hydrodistillation)	0.40%	HP-5 capillary column (25 m × 0.2 mm × 0.33 μm)	Helium	Gradient	Retention indices relative to hydrocarbon standards	Leaves	Duarte et al. (2007)
China	GC–MS	Essential oils of CyRh and processed product (extracted by hydrodistillation)	/	Agilent 19091S-433column (30 m × 250 μm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Sheng et al. (2013)
China-Jiangxi	GC–MS	Essential oils of CyRh and processed product (extracted by hydrodistillation)	/	DB -1701 quartz capillary column (30 m × 0.35 mm × 1.00 μm)	Helium	Gradient	/	Rhizomes	Hu et al. (2012)
China	GC–MS	Essential oils (extracted by hydrodistillation)	0.69%–1.25%	DB-1701 quartz capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Zhao et al. (2008)
China	GC–MS	Essential oils (extracted by hydrodistillation (HD), pressurized liquid extraction (PLE) and supercritical fluid extraction (SFE))	/	HP-5MS capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Tam et al. (2007)
China-Guangzhou	GC–MS	Essential oils (extracted by hydrodistillation and SFE)	2.3% (SFE), 0.8% (hydrodistillation)	SGE BP1 column (60 m × 0.25 μm)	Helium	Gradient	/	Rhizomes	Li et al. (2000)
China and India	GC–MS	Extraction with hexane/ ethyl acetate mixture (1:1), (+)-nootkatone	(+)-Nootkatone [30.47 μg/10 g (India), 21.72 μg/ 10 g (China)]	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	/	Rhizomes	Jaiswal et al. (2014)

Table 5 continued

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
Algeria	GC, GC–MS	Essential oils (extracted by hydrodistillation)	2.70%	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention index relative to *n*-alkanes	Rhizomes	Fenanir et al. (2021)
South Africa-Empangeni	GC, GC–MS	Essential oils (extracted by hydrodistillation)	0.20%	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices relative to *n*-alkanes (C_9–C_{24})	Rhizomes	Lawal and Oyedeji (2009)
South Africa-KwaDlangezwa	GC, GC–MS	Essential oils (extracted by hydrodistillation)	0.16%	DB-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices relative to *n*-alkanes (C_9–C_{24})	Rhizomes	Lawal and Oyedeji (2009)
South Korean-Seoul	GC, GC–MS	Essential oils (extracted by hydrodistillation)	2.70%	RTX-1 capillary column (60 m × 0.25 mm × 1.00 μm)	Helium	Gradient	Authentic sample	Rhizomes	Chang et al. (2012)
Iran-Ahwaz	GC, GC–MS	Essential oils (extracted by hydrodistillation)	1.50%	HP-5 MS capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Kovats retention indices calculated using *n*-alkanes (C_9–C_{23})	Aerial parts	Aghassi et al. (2013)
South-India	GC-FID, GC–MS	Essential oil (extracted by hydrodistillation and SPME)	0.11%	FSOT-RSL-200 fused silica column (30 m × 0.32 mm × 0.25 μm) and polar Stabilwax (30 m × 0.32 mm × 0.50 μm)	Helium	Gradient	Kovats indices relative to *n*-alkanes	Roots and Tubers	Jirovetz et al. (2004)
Brazil-Pará	GC-FID, GC–MS	Essential oils (extracted by hydrodistillation)	0.40%	DB-5 MS fused silica capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention indices relative to *n*-alkanes	Tubers	Zoghbi et al. (2008)
Saudi Arabia-Riyadh	GC-FID, GC–MS	Essential oils (extracted by hydrodistillation and extracted with diethyl ether from the aqueous distillate)	0.20%	Innowax FSC column (60 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Relative retention index calculated against a series of *n*-alkanes	Tubers	Al-Massarani et al. (2016)

Table 5 continued

Region	Method	Analytes	Yield	Column	Mobile Phase	Elution program	Detection/ Chromogenic conditions	Plant part	References
Tunisia-Kebili	GC-FID, GC–MS	Essential oils (extracted by hydrodistillation), F1: *n*-pentane, F2: *n*-pentane/diethyl ether (95/5) and F3: diethyl ether further fractionated from essential oils	0.5 ± 0.3%	HP-1 column (50 m × 320 μm × 0.5 μm), HP-innowax columns (60 m × 320 μm × 0.5 μm)	Helium	Gradient	Retention Indices relative to *n*-alkanes	Tubers	Essaidi et al. (2014)
Turkey	HS–SPME–GC–MS	Essential oils (HS-SPME extraction)	/	Innowax FSC column (60 m × 0.25 mm × 0.25 mm)	Helium	Gradient	Relative retention index (RRI) relative to a series of *n*-alkanes	Root	Eröz Poyraz et al. (2018)
China	HS–SPME–GC–MS	Volatile/heat-labile components (SPME extraction)	/	HP-5 capillary column (30 m × 0.25 mm × 0.25 μm)	Helium	Gradient	Retention index calculated against alkane standard solutions of C_8–C_{20} and C_{21}–C_{40}	Rhizomes	He et al. (2018)

Qualitative and semi-quantitative analyses of EOCR by GC–MS were performed and the essential oils from different regions were compared to identify the intrinsic material basis for their distinctions. Volatile oils of *C. rotundus* were mostly extracted by hydro-distillation (HD) (Kilani et al. 2008b; Ghannadi et al. 2012; Yagi et al. 2016; Abo-Altemen et al. 2019), in addition to supercritical fluid extraction (SFE) (Feng et al. 2006; Tam et al. 2007; Cao and Ou 2015), solid phase micro extraction (SPME) (Tam et al. 2007; Eröz Poyraz et al. 2018; He et al. 2018), pressurized liquid extraction (PLE) (Tam et al. 2007), mixed solvent extraction by ultrasound (Lin et al. 2006) and *n*-hexane extraction (Komai and Tang 1989). The yield of volatile oil varies dramatically depending on the region and extraction method. For example, by using the hydro-distillation method, the yield of volatile oil extracted from the rhizomes of *C. rotundus* in Seoul, South Korea was 2.7% (Chang et al. 2012), while the yield of essential oil extracted by the same method from the tubers in Isfahan, Iran, was only 0.2% (Ghannadi et al. 2012). The volatile oil, the characteristic and flavor component, has been taken as the crucial marker for the quality control of *C. rotundus*. Thus, the ChP stipulates that the content of volatile oil should not be less than 1.0% (mL/g) (China Pharmacopoeia Committee 2020). It can be concluded from a number of literature that the DB-5 capillary column (30 m × 0.25 mm × 0.25 μm) and HP-5 MS capillary column (30 m × 0.25 mm × 0.25 μm) are commonly selected as GC columns for the analysis of EOCR (Lawal and Oyedeji 2009; Ghannadi et al. 2012; Hu et al. 2017; Fenanir et al. 2021). It is interesting to note that investigations have shown that the volatile components of the aerial parts of *C. rotundus* are quite different from those of its rhizomes (Aghassi et al. 2013; Elezabeth and Arumugam 2014).

Flame ionization detector (FID) has gained great popularity over recent years for its excellent response and stable signal for hydrocarbons, as well as simple operation and low cost compared to MS (Jirovetz et al. 2004; Zoghbi et al. 2008). For example, the GC-FID technique was used by Al-Massarani et al. for analyzing the volatile components of *C. rotundus* tubers originating from India, Brazil and Saudi Arabia (Al-Massarani et al. 2016).

HPLC/UHPLC analysis

Liquid chromatography (LC), including HPLC and UHPLC, is frequently and consistently utilized as an effective and excellent means for the identification and quantitative determination of compounds due to its accessibility, ease of operation, high sensitivity and reproducibility, good resolution and linearity, and the ability to analyze a diverse range of components. It is one of the common techniques used for the quality assessment of *C. rotundus*. In practical terms, certain conditions of analysis, consisting of analytes type, mobile phase, mobile phase flow rate, column temperature, column type, eluent program and detector, are critical factors affecting HPLC analysis. Supplementary Table S18 reveals the detailed conditions for the HPLC approach with regard to the analyses of *C. rotundus*.

It could be found that most of the analytes subjected to LC analysis of *C. rotundus* are the major sesquiterpenoid components, as well as the phenolic components. The mobile phases are commonly methanol–water or acetonitrile–water, with the addition of 0.1–0.5% formic acid, acetic acid, or trifluoroacetic acid to the aqueous phase. Varied columns and different detectors (such as PDA, DAD and MS) are now frequently equipped for the qualitive or quantitative analyses.

As is reported, the contents of mesocyperusphenol A (**499**), scirpusins A (**494**) and β-sitosterol (**422**) were evaluated in *C. rotundus* from different regions in China by UPLC and HPLC. The results indicated that the content of active ingredients in *C. rotundus* from Shandong, was relatively higher than those of other regions, revealing the necessity of selecting authentic and genuine herbs (Cao and Ou 2015; Deng et al. 2016). Zhao et al. established an HPLC method for fingerprinting the chemical components in the methanolic extracts of eight batches of *C. rotundus* from different regions, as well as similarity evaluation and clustering analysis (Zhao et al. 2008). Deng et al. have developed an approach for effective and rapid affinity-based screening of natural α-glucosidase inhibitors directly from *C. rotundus* extracts by utilizing an immobilized enzyme technique integrated with UHPLC-QTOF-MS analysis (Deng et al. 2019). Also, tissue-specific metabolite analyses of *C. rotundus* from India and China by laser microdissection, UHPLC-QTOF-MS/MS and additional GC–MS have

Table 6 Ingredients in essential oils of *C. rotundus* with relative contents higher than 1% and identification frequency above 3

Compound (No.)	Identification frequency	Compound (No.)	Identification frequency
Caryophyllene oxide (**241**)	24	Cyperotundone (**154**)	4
Cyperene (**165**)	23	α-Humulene (**266**)	4
α-Cyperone (**111**)	21	Mustakone (**256**)	4
β-Selinene (**97**)	14	α-Cubebene (**319**)	4
trans-Pinocarveol (**28**)	13	α-Calacorene (**183**)	4
Aristolone (**296**)	13	Spathulenol (**230**)	4
α-Copaene (**257**)	12	Rotundene (**251**)	4
Myrtenol (**37**)	12	α-Gurjunene (**214**)	4
Longiverbenone (**284**)	12	*γ*-Muurolene (**191**)	3
α-Pinene (**38**)	11	Pinocarvone (**29**)	3
β-Pinene (**39**)	10	Isocyperol (**96**)	3
Isolongifolen-5-one (**291**)	9	Methyl (*Z*)-5,11,14,17-eicosatetraenoate (**545**)	3
Humulene epoxide II (**264**)	8	Isolongifolene (**293**)	3
Nootkatone (**235**)	7	Isoaromadendrene epoxide (**226**)	3
Myrtenal (**35**)	7	Cyperene epoxide (**161**)	3
Verbenone (**30**)	7	8-Oxo-9*H*-cycloisolongifolene (**305**)	3
α-Terpineol (**17**)	6	α-Ylangene (**262**)	3
α-Selinene (**131**)	6	α-Longipinene (**286**)	3
4-Oxo-α-ylangene (**261**)	6	Valencene (**237**)	3
Limonene (**1**)	6	*trans*-Carveol (**12**)	3
Aromadendrene, dehydro- (**215**)	6	Eudesma-2,4,11-triene (**124**)	3
β-Caryophyllene (**242**)	5	Patchoulenone (**152**)	3
1,8-Cineole (**93**)	5	*allo*-Aromadendrene (**228**)	3
Aromadendrene epoxide (**225**)	4		

been conducted and the outcomes demonstrated that the content of (+)-nootkatone **(235)** in *C. rotundus* of India (30.47 *μ*g/10 g), was higher than that of China (21.72 *μ*g/10 g) (Jaiswal et al. 2014). Furthermore, LC–ESI–MS/MS was employed to characterize the phytochemical composition of the total oligomeric flavonoid (TOF) of *C. rotundus* and simultaneously to determine its total flavonoid and total phenolic (TPC) content (Kandikattu et al. 2015).

Other analytical methods

In other aspects, a simple, sensitive and effective HPTLC and HPLC method (245 nm) was established to verify the validity for quantification of solavetivone (**302**), which had been initially isolated from *C. rotundus* (Priya Rani and Padmakumari 2012). With the help of TLC, UV (Ultraviolet and visible spectrophotometer) and IR (Grating Infrared spectrophotometer), Samariya and Sarin have analyzed qualitatively four compounds obtained by PTLC, namely quercetin (**377**), kaempferol (**376**), myricetin (**380**) and catechin (**399**). By UV spectrophotometer as well as other techniques, quercetin, kaempferol and myricetin have been analyzed quantitatively. A conclusion was reached that the total flavonoid content in the leaves of *C. rotundus* was higher compared to the roots, with the total quercetin content also higher than the roots (Samariya and Sarin 2013). In addition, PIXE and ICP-MS techniques have been applied to analyze qualitatively and quantitatively some inorganic elements in *C. rotundus*. These include Li, Al, Cl, K, Ca,

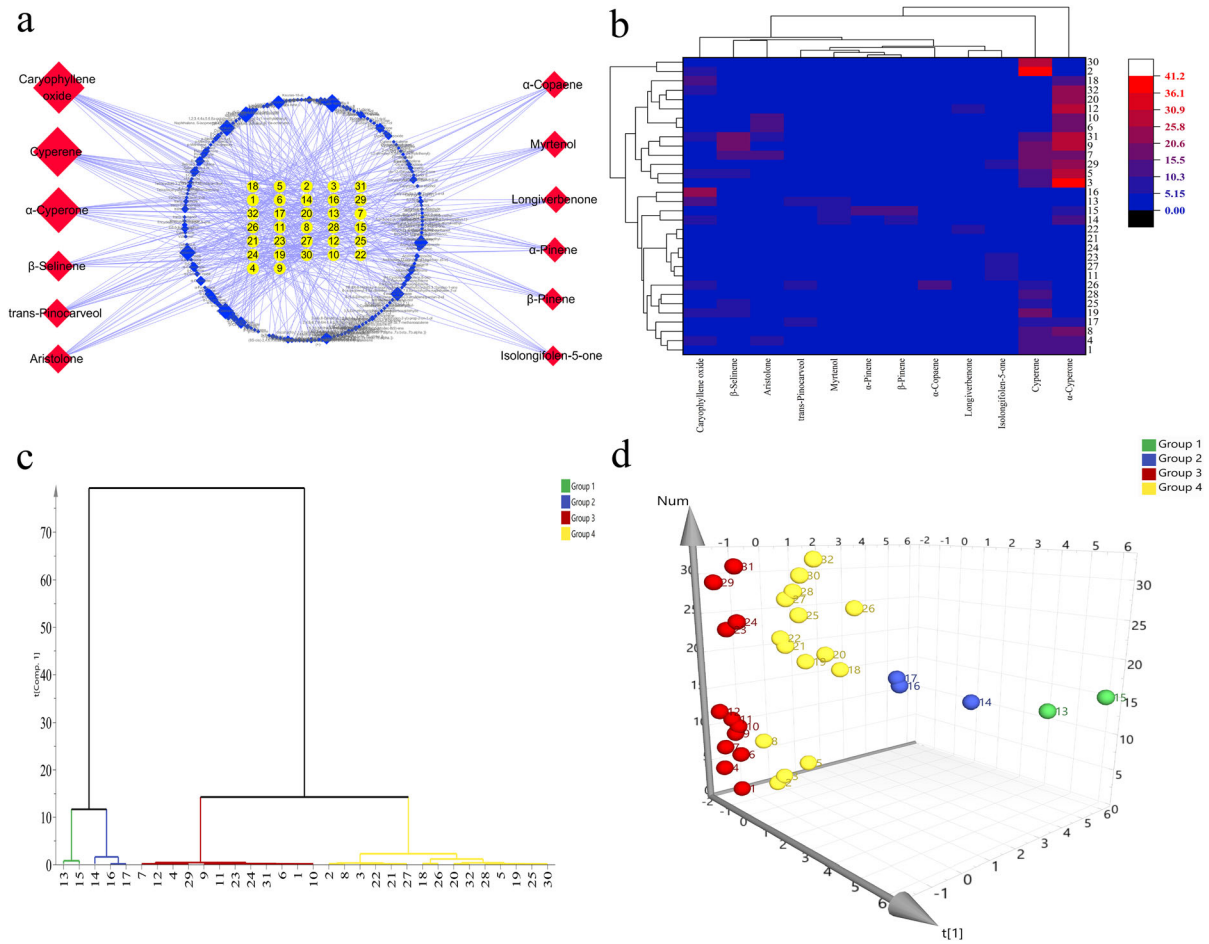


Fig. 7 Multivariate statistical analysis on thirty-two essential oils of *C. rotundus* from different regions. **a** "Region-Component" network; **b** Heatmap analysis; **c** HCA analysis; **d** PCA analysis

Ti, V, Cr, Mn, Fe, Co, Ni, Cu and Zn (supplementary Table S18) (Rao et al. 2019).

Multivariate statistical analysis of the essential oil of *C. rotundus*

Up until now, numerous works have systematically carried out the analysis regarding EOCR from different countries on account of the worldwide distribution (El-Gohary 2004; Kubmarawa et al. 2005; Kilani et al. 2008b; Zoghbi et al. 2008; Lawal and Oyedeji 2009; Chang et al. 2012; Nidugala et al. 2015; Yagi et al. 2016; Janaki et al. 2018; Abo-Altemen et al. 2019; Samra et al. 2020; Fenanir et al. 2021; Qu et al. 2021). The essential oil, the extremely main and valuable bioactive substance of *C. rotundus*, is contained in the rhizome, tuber and aerial parts (Zoghbi et al. 2008; Kilani-Jaziri et al. 2009; Chang et al. 2012). Details of the chemical composition and structure of EOCR are presented in the supplementary Tables S10–17 and supplementary Fig. S1–23. Moreover, chemical constituents that have been reported to be present in EOCR by at least two publications were considered and included in the tables.

In this section, a comprehensive summary of over thirty articles of literature concerning the essential oil profiling of *C. rotundus* via the GC–MS is presented in detail as shown in supplementary Table S19. The components displayed only include those with relative content greater than 1%, which were then regarded as essential ingredients (Table 6). The numbers in Fig. 7

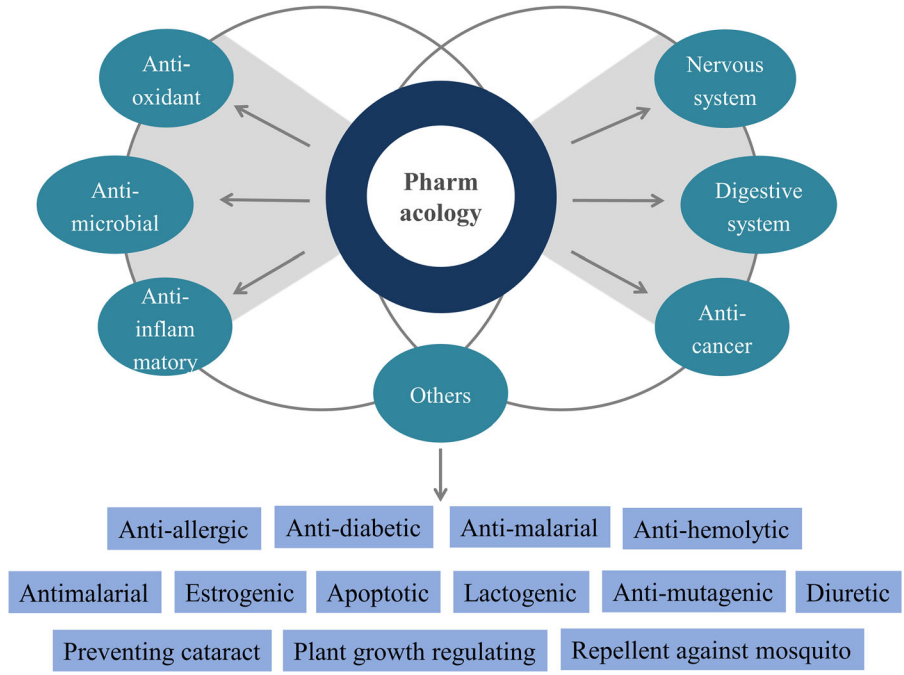


Fig. 8 The diagram of pharmacological properties of *C. rotundus*

represent the corresponding region of the *C. rotundus* and details are listed in supplementary Table S21. These references contain only the GC–MS studies of *C. rotundus* tubers and rhizomes by hydrodistillation. Neither the studies of aerial parts of *C. rotundus*, nor the studies with other analytical means such as SFE, SPME, ultrasonic extraction with organic reagents and GC-FID are included, so as to allow for a better comparative effect. The detailed methods for multivariate statistical analysis of the essential oil were provided in the supplementary materials.

Figure 7a visually indicates that the types of constituents in EOCR vary along with the regions, and it may be possible for the same components to occur simultaneously in *C. rotundus* from different countries, uncovering the difficulty and complexity of quality control and assessment for *C. rotundus* at present. The figure outwardly demonstrated that the top twelve key compounds in EOCR are caryophyllene oxide (**241**), cyperene (**165**), α-cyperone (**111**), *β*-selinene (**97**), *trans*-pinocarveol (**28**), aristolone (**296**), α-copaene (**257**), myrtenol (**37**), longiverbenone (**284**), α-pinene (**38**), *β*-pinene (**39**), isolongifolen-5-one (**291**).

The outcomes of HCA (Fig. 7c) and PCA (Fig. 7d) analysis revealed that the thirty-two batches of *C. rotundus* could be clustered into four groups, in which NO14, NO16, NO17 were classified as group I, NO2, NO8, NO3, NO22, NO21, NO27, NO18, NO26, NO20, NO32, NO28, NO5, NO19, NO25, NO30 were treated as group II, NO13, NO15 were classified as group III, and the remaining batches were clustered into group IV. This phenomenon indicates that the intrinsic material bases of the *C. rotundus* originating from different regions of the same country are not identical. The quality of *C. rotundus* from diverse nations also varies. Especially, the main volatile ingredients, such as α-cyperone and cyperene, can also be strongly affected by their geographical origin. This variability might be closely associated with hereditary factors, growth year, storage time, storage conditions, plant parts, herbal processing or not, and environmental factors, specifically soil composition, climatic factors, seasonality and circadian cycle, all of which may impact the qualitative and quantitative profiling of components in the essential oils.

A conclusion can be easily drawn from Fig. 7b, that α-cyperone (**111**) and cyperene (**165**) exist in almost all regions with relatively high contents, and they

possess a variety of pharmacological activities (Weenen et al. 1990a; Khan et al. 2011; Jung et al. 2013), and hence, they were frequently recommended as the quality control marker of *C. rotundus*. Besides, caryophyllene oxide (**241**), β-selinene (**97**) and aristolone (**296**) also play important roles in EOCR (Ghannadi et al. 2012; Richa and Suneet 2014).

Pharmacology

There have been more than ten previous reviews which refer to the pharmacological effects of *C. rotundus*, as well as more than hundreds of studies on its pharmacological properties with the first dating back to 1959. Hence, the pharmacology of *C. rotundus* has been researched thoroughly, and this section intends to comprehensively summarize the pharmacological actions of *C. rotundus*, like anti-inflammatory, antioxidant, apoptotic, antibacterial, digestive system effects, neuroprotective effects, based on the experiments in vitro, in vivo and in clinical trials (Fig. 8, supplementary Table S22). Additionally, novel indications and hot spots of research in recent years are also included in this summary.

Anti-oxidant activity

Components in *C. rotundus*, such as phenolic acids, alkaloids, quinones, essential oil and sesquiterpenoids have shown excellent antioxidant activity (Kandikattu et al. 2015), especially phenolic compounds, including flavonoids, coumarins, and polyphenols (Kilani-Jaziri et al. 2011; Soumaya et al. 2014). For isolated compounds, nootkatone (**235**) exerted the strongest DPPH radical scavenging capacity, with IC_{50} valued 4.81 μg/mL followed by aristolone (**296**) and solavetivone (**302**), whose IC_{50} was valued at 5.28 μg/mL and 6.82 μg/mL respectively (Priya Rani and Padmakumari 2012). Compared with ethanol and ethyl acetate extracts, aqueous extract of *C. rotundus* has exhibited the strongest scavenging activity as shown by DPPH assay, with an IC_{50} value of 418.74 μg/mL (Mohamed et al. 2021). In addition to scavenging DPPH free radicals, *C. rotundus* also showed scavenging ability on hydroxyl radical, superoxide radical, xanthine/xanthine oxidase and others (Kilani et al. 2008b).

It is well known that the oxidative stress plays a vital role in diseases such as epilepsy, neurodegenerative disorders (Alzheimer's disease and Parkinson's disease) (Lee et al. 2010; Rabiei et al. 2013), non-steroidal anti-inflammatory drug-induced gastric mucosal damage (Thomas et al. 2015), hepatic injury (Mohamed 2015) and diabetes (Raut and Gaikwad 2006). *C. rotundus* shows potential activity in treatments of these oxidative stress-related disease, owing to its antioxidative activity by regulating the levels of some biological enzymes (SOD, HO-1, GSH-Px), and cell factors (MDA) (Baek and Lee 2016). It is recorded that the rhizome extract of *C. rotundus* can improve the level of SOD and decrease the level of MDA in pentylentetrazole (PTZ)-induced mice brain, exerting its oxidation resistance property. Epileptic seizure in mice was alleviated after the treatment with *C. rotundus* (Khalili et al. 2011).

Anti-microbial activity

The antimicrobial activities of *C. rotundus* involves anti-bacterial, anti-fungal and anti-viral effects (Al-Massarani et al. 2016; Samra et al. 2020). *C. rotundus* inhibited *Streptococcus mutans* by suppressing the bacterial growth, adherence activity and water-insoluble glucan synthesis, and, reducing acid production (Yu et al. 2007). Studies have found the antibacterial activity of *C. rotundus* among different bacterial species, no matter whether they are Gram-positive or Gram-negative (Kabbashi et al. 2015). It has however been revealed that inhibition of Gram-positive bacteria is more sensitive than that of Gram-negative bacteria owing to the differences in the lipopolysaccharides of their cell walls (Ouattara et al. 1997; Kilani et al. 2005a). The anti-viral effect of *C. rotundus* have been demonstrated only against hepatitis B virus (Parvez et al. 2019).

Recently, the screening and prediction of active constituents of herbs by computer simulation technology have become a research hotspot. As coronavirus disease 2019 (COVID-19) has spread throughout the world, screening of natural products against M^{pro} of SARS-CoV-2 has attracted great attention. Subsequently, components of *C. rotundus* were screened by molecular docking and successively compared with standard drugs to value the binding of protein–ligand interactions. Molecular dynamics was used to assess that binding, and finally pharmacokinetic properties

and safety profiles were measured. From this study, β-amyrin (**411**) and stigmasta-5,22-dien-3-ol (**424**) were selected as the molecules that potentially inhibit SARS-COV-2 M^{pro} and thus implied their potential therapeutic effect against COVID-19 (Kumar et al. 2021).

Anti-inflammatory activity

In previous studies of pharmacologic activities of *C. rotundus*, the extracts and its isolated compounds have been demonstrated to reduce the levels of the inflammatory mediators, cytokines, and transcription factors, like 5-LOX, COX-2, PGE2, IL-1, IL-6, TNF-α (Seo et al. 2001; Jung et al. 2013; Ibrahim et al. 2018). It has also been shown that they could reduce the inflammatory response by suppressing the regulation of the NF-κB signal pathway and down-regulating AP-1 activation (Khan et al. 2011; Jung et al. 2013; Choi et al. 2014; Shin et al. 2015; Ibrahim et al. 2018). Furthermore, the generation of NO, which reflects the degree of inflammation at the cellular level, can be reduced after treatment with *C. rotundus* rhizome extract by suppressing the expression of iNOS in LPS-stimulated RAW 264.7 cells (Tsoyi et al. 2011). The extent of ear edema, cellular infiltrates and keratinocyte hyperproliferation were depressed in arachidonic acid and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced mice after the administration of *C. rotundus* rhizome ethanolic extract (Rocha et al. 2020).

The sesquiterpenoids components of *C. rotundus*, to be specific, were found to possess pronounced anti-inflammatory effect (Tsoyi et al. 2011), particularly, nootkatone **(235)**, α-cyperone **(111)**, valencene **(237)**, and β-selinene **(97)** (Khan et al. 2011).

The anti-inflammatory function of *C. rotundus* in experimental studies has implied that it has the potential to cure inflammatory skin disorders (Rocha et al. 2020) and peritonitis (Dang et al. 2011).

Central Nervous system activity

C. rotundus has been reported to exert neuroprotective (Lee et al. 2010; Hemanth Kumar et al. 2013; Kim et al. 2013; Jebasingh et al. 2014; Dabaghian et al. 2015; Kandikattu et al. 2017; Sutalangka and Wattanathorn 2017; Hussein et al. 2020), antidepressant (Jia and Zou 2014; Lin et al. 2015; Zhou et al. 2016a, 2016b; Hao et al. 2017), anti-Alzheimer's (Rabiei et al. 2013; Mehdizadeh et al. 2017; Shakerin et al. 2020), anticonvulsant (Shivakumar et al. 2009; Khalili et al. 2011), analgesic (Pal et al. 2009; Ahmad et al. 2012; Imam and Sumi 2014), and neuromodulatory (Ha et al. 2002; Rafe et al. 2019) effects. Antidepressant and neuroprotective effects are two dominant activities of *C. rotundus* with regard to the CNS system. The ethanol extract and water extract of *C. rotundus* have shown antidepressant-like action by the tail suspension test (TST) and the forced swim test (FST) in murine models (Jia and Zou 2014; Hao et al. 2017). Ethanol extract of *C. rotundus* at doses of 200 and 400 mg/kg effectively protected against cognitive impairment, locomotor activity and muscle coordination deficits induced by sodium nitrite-induced hypoxic injury in rats (Jebasingh et al. 2014). Hydro-alcoholic extract of *C. rotundus* prolonged the latency of seizure and reduced the duration of seizure in mice (Khalili et al. 2011).

Digestive system effects

The role of *C. rotundus* in regulating the digestive system is in general agreement with TCM and there have been numerous reports concerning the hepatoprotective (Kumar and Mishra 2005; Mohamed 2015; Oh et al. 2015; Parvez et al. 2019), gastroprotective(Thomas et al. 2015), anti-diarrhoeal (Uddin et al. 2006), anti-infectious diarrhea (Daswani et al. 2011) and anti-gastric ulceration (Zhu et al. 1997) effects of *C. rotundus*. For example, Parvez et al. have demonstrated a promising hepatoprotective effect of *C. rotundus* in vivo experiments in rats and also proven that the *n*-butanol and aqueous fractions of *C. rotundus* rhizomes exhibit the most prospective activity against HBV in vitro in DCFH-damaged HepG2 cells (Parvez et al. 2019). Furthermore, *C. rotundus* can dramatically inhibit aspirin-induced gastric ulceration and lipid peroxidation in ulcerated rats in a dose-dependent manner (Thomas et al. 2015). After treatment with *C. rotundus* methanol extracts, the frequency of diarrhea onset in mice decreased (Uddin et al. 2006), and at the same time, the cytoprotective effect of the aqueous decoction of *C. rotundus* on the ethanol-induced gastric injury was verified (Zhu et al. 1997).

Anti-cancer activity

In recent years, the antitumor activity of *C. rotundus* has gradually attracted the attention of researchers and become a hot direction of researches, including those with potential effects against cervical cancer (Mannarreddy et al. 2017; Saad et al. 2018; Susianti et al. 2018; Lin et al. 2019), breast cancer (Park et al. 2014; Mannarreddy et al. 2017; Wang et al. 2019; Simorangkir et al. 2019; Ma et al. 2020; Samra et al. 2020), ovarian cancer (Ryu et al. 2015; Ahn et al. 2015), esophagus cancer (Al-Shammari et al. 2021), hepatocellular carcinoma (Parvez et al. 2019; Samra et al. 2020), human rectal cancer (Mannarreddy et al. 2017; Al-Shammari et al. 2021), prostate cancer (Mannarreddy et al. 2017; Samra et al. 2020) and colorectal cancer (Park et al. 2014; Ahn et al. 2015; Ryu et al. 2015; Al-Massarani et al. 2016; Ying and Bing 2016; Mannarreddy et al. 2017; Abdulghany et al. 2018; Susianti et al. 2018; Lin et al. 2019; Simorangkir et al. 2019; Wang et al. 2019; Ma et al. 2020; Samra et al. 2020; Al-Shammari et al. 2021). The ethanol extract of *C. rotundus* (EECR) has been demonstrated to possess a potential effect against human cervical cancer and breast cancer in HeLa human cervical carcinoma cells and MCF-7 cells (Lin et al. 2019; Simorangkir et al. 2019). The EOCR was found to have cytotoxic activity against the HeLa cervical cells (Susianti et al. 2018).

Others

In addition to the above, studies have also uncovered the anti-allergic (Jin et al. 2011), antidiabetic (Raut and Gaikwad 2006; Lemaure et al. 2007; Singh et al. 2015; Majeed et al. 2022), antihemolytic (Kilani et al. 2005a), antimalarial (Weenen et al. 1990a, 1990b; Thebtaranonth et al. 1995), antimutagenic (Kilani et al. 2005a), apoptotic (Kilani et al. 2008a, 2008b; Soumaya et al. 2014), estrogenic (Hendri et al. 2016; Park et al. 2019), repellent against mosquito (Singh et al. 2009; Al-Massarani et al. 2016), lactogenic (Badgujar and Bandivdekar 2015), against urinary tract infection (Sharma et al. 2014) and diuretic effects (Sripanidkulchai et al. 2001) of *C. rotundus.*

Toxicology

Given the importance of understanding the toxicity of herbal medicines to facilitate their safe use, the toxicological studies in vivo and in vitro of the extracts, essential oil, and isolated compounds from *C. rotundus* have been summarized and presented in supplementary Table S23.

Numerous acute toxicity tests have shown that essential oil (Biradar et al. 2010), *n*-hexane extract (Lemaure et al. 2007), ethanol extract (Akperbekova and Abdullaev 1966; Thanabhorn et al. 2005; Ahmad M et al. 2013; Okwu et al. 2015; Singh et al. 2015; Al-Snafi 2016; Rajakrishnan et al. 2020; Shakerin et al. 2020; Al-Awar and Alqabbani 2021), methanol extract (Soumaya et al. 2013; Imam and Sumi 2014; Kabir et al. 2019), and water extract (Krisanapun et al. 2012; Badgujar and Bandivdekar 2015) of *C. rotundus* didn't arise any behavioral, biochemical, or histological alterations either in mice or in rats. And, there was a subacute toxicity test revealing that the ethanol extract of the rhizomes of *C. rotundus* didn't cause any mortality or behavioral changes after an administration of 1,000 mg/kg daily over 14 days (Thanabhorn et al. 2005).

However, the extract of *C. rotundus* showed significant cytotoxicities to various cancer cells, including L1210 (Kilani et al. 2008a), MCF-7 (Mannarreddy et al. 2017), HeLa (Mannarreddy et al. 2017), HepG2 (Mannarreddy et al. 2017), PC-3 (Mannarreddy et al. 2017), HT-29 (Mannarreddy et al. 2017), MDA-MB 231 (Ma et al. 2020), and MDA-MB 468 (Ma et al. 2020) cells, without any observable cytotoxic effects against normal cells, such as LO2 (Song et al. 2016), MCF-12A (Mannarreddy et al. 2017), HGF (Moein et al. 2018), and BV-2 cells (Huang et al. 2018). It is worth mentioning that the essential oil of *C. rotundus* didn't show any significant inhibitory effects on SH-SY5Y cells viability at the concentration of 50–150 μg/mL, unless above 150 μg/mL (Hu et al. 2017). Similarly, 10–100 μg/mL 70% ethanolic extract of *C. rotundus* didn't exert any significant cytotoxicities against SH-SY5Y cells, instead of a significant decrease of the cell's viability once the final concentration was above 100 μg/mL (Hemanth Kumar et al. 2014). And, 25–100 mg/mL of the water decoction of *C. rotundus* didn't affect PC12 cell's viability unless the administration concentration was up to 200 mg/mL (Lee et al. 2010).

As for other aspects, 4,11-selinnadien-3-one, namely α-cyperone (**111**), from *C. rotundus* was known to be toxic to the bee larvae (*Apis florea*) with an IC_{50} of 10.8 ppm (Visetson et al. 2001). And, khellin (**403**) and visnagin (**404**) were reported to induce *Artemia salina* LEACH mortality in the brine shrimp lethality test (Sayed et al. 2007). In general, a conclusion can be safely drawn that *C. rotundus* is deemed safe enough for further development and utilization.

Conclusion and future perspectives

This review provides a comprehensive summary regarding distribution, synonyms, traditional uses, data mining of application in TCM, phytochemistry, isolation, analysis and identification methods, pharmacology and toxicology of *C. rotundus* to provide detailed and scientific evidence for its modern indications and intensive clinical applications in treatments of different diseases.

Traditional uses, chemical components and pharmacological activities

C. rotundus have various traditional applications in different nations, whereas the common important uses are for gastrointestinal discomforts, mental disorders, menstrual disorders in women and skin problems. Notably, a data mining of TCM prescriptions containing *Cyperi rhizoma* draws the generally same conclusion as the modern pharmacological research, which concluded that CyRh was commonly prescribed for the treatment of diseases of (I) the Spleen system, (II) the women's menstrual, leucorrhea and miscellaneous diseases, (III) the fetuses, parturients and their diseases and (IV) the Brain system, (V) the Liver system, corresponding to (1) the digestive system diseases, (2) the nervous system and (3) the gynecological diseases in the western medicinal system. As shown in Table 3, the modern pharmacological effects and bioactivities of the extracts, fractions and compounds related to the traditional uses of *C. rotundus* in TCM are summarized.

The main constituents of *C. rotundus* include essential oil, sesquiterpenoids (with diverse skeletons such as eudesmane, patchoulane, cadinene, caryophyllene types), flavonoids, phenolic acids, saponins, alkaloids, and etc. And the essential oil is the most important and bioactive substance of *C. rotundus*. Cyperene (**165**), α-cyperone (**111**), caryophyllene oxide (**241**), *β*-selinene (**97**), *trans*-pinocarveol (**28**), aristolone (**296**) are the vitally important components of the essential oil in the clue of their relative high contents in this medicinal plant as illustrated in the re-analyzed result (Fig. 7 and supplementary Tables 19–21) by multivariate statistical analysis of EOCRs. Furthermore, α-cyperone (**111**), nootkatone (**235**), isocyperol (**96**), cyperotundone (**154**), valencene (**237**) and other compounds of iridoid glycosides, flavonoids and saponins were isolated and considered to be the main active ingredients of *C. rotundus*. These so-called main constituents have been evaluated to exhibit extensive pharmacological activities as mentioned above. Interestingly, cyperene (**165**), α-cyperone (**111**), isocyperol (**96**), cyperotundone (**154**), cyperol (**127**) not only present in *C. rotundus*, but also existed specially in other plants of *Cyperus* species, such as *C. esculentus* L., *C. distans* L.f., and *C. articulatus* L. This phenomenon to some extent explains that why these *Cyperus* plants with similar chemical components exhibit similar pharmacological activities (including the treatment potentials for gastrointestinal disorders, menstrual irregularities, and inflammatory diseases) (Taheri et al. 2021).

Different extracts and fractions of *C. rotundus* exhibited distinct activities, which could be attributed to the structural diversity and the uneven distribution of the phytoconstituents present in these extracts and fractions. TOF extract exhibited the strongest antioxidant activity, followed by the other solvent extracts in the order of ethyl acetate > methanol extract > water extract (Kilani et al. 2008a, 2005b; Kilani-Jaziri et al. 2011). The reason may be the intrinsic contents of the common antioxidants of phenolic compounds such as flavonoids, tannins and coumarins in those extracts (Hussein et al. 2020). The anti-breast cancer activity of EECR was stronger than MECR in the human breast carcinoma cell (MDA-MB-231) model (Park et al. 2014). The anti-ovarian cancer activity of the *n*-hexane fraction was more potent than that of the ethyl acetate (EtOAc) fraction of EECR followed by EECR in the human ovarian cancer cell (A2780) model. The IC_{50} values of the *n*-hexane and EtOAc fractions were different among different cancer cell lines (Ahn et al. 2015). Moreover, *n*-butanol and aqueous fractions of *C. rotundus* showed significant hepatoprotective

activity against DCFH-induced HepG2 cytotoxicity compared to other fractions (e.g., hexane, chloroform, and EtOAc fractions). Meanwhile, the EtOAc fraction exhibited highly promising anti-HBV activity, followed by *n*-butanol and aqueous fractions of *C. rotundus* (Parvez et al. 2019).

In conclusion, the chemical constituents of *C. rotundus* could be considered to be mostly from the essential oil, the non-aqueous solvent-soluble (eg. ethanol, methanol, ethyl acetate) and the water-soluble components. Different extracts and fractions of *C. rotundus* exhibited distinct activities, which could be attributed to the structural diversity and the uneven distribution of the phytoconstituents present in these extracts and fractions. It is noteworthy that a number of literatures have reported the activities of *C. rotundus* concerning nervous system diseases, digestive system disorders, gynecological disorders, both in vivo and in vitro. To some extent, this phenomenon validates the diverse traditional uses of *C. rotundus*. However, there are no available clinical trials demonstrating the activities of *C. rotundus* in these aspects, and even the in vivo pharmacological evaluations concerning the uses of *C. rotundus* in the treatment of gynecological diseases, instead of the numerous in vitro experiments conducted in several cancer cells including HepG2, HeLa, MCF-7, MDA-MB-468, MDA-MB-231, A2780, SKOV3, OVCAR-3, Hec1A, and Ishikawa cells. Consequently, in vivo or even clinical trials are needed in the future for further validation of the efficacies of *C. rotundus* in light of its traditional uses.

Deficiency and prospect

Due to its wide distribution, the chemical composition of *C. rotundus* varies greatly along with the regions, and the variations in chemical composition directly led to the differences in the pharmacological effects of *C. rotundus*. This makes quality control of *C. rotundus* challenging, especially the pharmacological activity-associated global quality control standards for *C. rotundus*, which unfortunately are not yet available. Again, there was little in-depth research on the potential of those bioactive components for clinical uses. And numerous further evidence of their pharmacological effects is still urgently needed. These remind us that the diverse pharmacological activities of *C. rotundus* should be fully developed and utilized, and the global quality control methods for *C. rotundus* should be established accordingly. It is also advisable to study the uses of *C. rotundus* from different countries separately, where the chemical composition of *C. rotundus* differs and their pharmacological activities vary greatly. In addition, it is currently challenging to identify the functional factors of components in herbal medicine for a specific disease and to assess the contribution weights of functional factors due to the diversity of phytoconstituents of herbal medicines and the complexity of their mechanisms of action. To overcome these obstacles, instead of the classic workflow of phytochemical isolation and purification followed by activity screenings, several statistical methods (e.g., fingerprint-efficacy relationship) and modern molecular networking technologies (network pharmacology, molecular docking, or molecular dynamics simulation), are encouraged to perform a virtual screening of the active phytochemicals before further phytochemistry and pharmacological studies.

Recently, as COVID-19 has spread throughout the world, studies using molecular docking and molecular dynamics have demonstrated the inhibition effect of *C. rotundus* against SARS-CoV-2 M^{pro} (Kumar et al. 2021) and implied its potential as a therapeutic agent for COVID-19. It might be worthwhile to conduct an in-depth study on the contribution of *C. rotundus* against COVID-19 pandemic in the near future.

Acknowledgements This work was financially supported by a grant (No. 21ZYJDJC00080) from the Tianjin Committee of Science and Technology of China, the National Key Research and Development Project of China (No. 2018YFC1707904, 2018YFC1707905 and 2018YFC1707403) and the Important Drug Development Fund, Ministry of Science and Technology of China (No. 2018ZX09735-002).

Authors contribution BXX, RSH and JXL were responsible for the data collection. The design of the whole review and critical revision of the manuscript were done by HHW, BXX and NAM, LHZ and HHW assisted with the analysis and interpretation of the data. BXX and RSH were responsible for drafting the manuscript. The drawing of the figures was done by BXX.

Declarations

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

References

Abdulghany Z, Mahmood N, Tawfeeq A, Yassen N (2018) *Cyperus rotundus* tubers extract inhibits stem cell markers expression in cervical and human glioblastoma cancer cell lines. Iraqi J Med Sci 16:159–165

Abo-Altemen RA, Al-Shammari AM, Shawkat MS (2019) GC-MS analysis and chemical composition identification of *Cyperus rotundus* L. from Iraq. Energy Procedia 157:1462–1474

Aeganathan R, Rayar A, Ilayaraja S, Prabakaran K, Manivannan R (2015) Antioxidant, anti–microbial evaluation and GC-MS analysis of *Cyperus rotundus* L. rhizomes chloroform fraction. Am J Ethnomed 3:14–20

Aghassi A, Naeemy A, Feizbakhsh A (2013) Chemical composition of the essential oil of *Cyperus rotundus* L. from Iran. J Essent Oil Bear Plants 16:382–386

Ahmad M, Mahayrookh M, Rehman AB, Jahan N (2012) Analgesic, antimicrobial and cytotoxic effect of *Cyperus rotundus* ethanol extract. Pak J Pharmacol 29:7–13

Ahmad M, Mahayrookh M, Rehman AB, Jahan N (2013) Toxicological and biochemical evaluation of ethanolic crude extract of *Cyperus rotundus*. Int J Pharm Pharm Sci 5:538–544

Ahn JH, Lee TW, Kim KH, Byun H, Ryu B, Lee KT, Jang DS, Choi JH (2015) 6-Acetoxy cyperene, a patchoulane-type sesquiterpene isolated from *Cyperus rotundus* rhizomes induces caspase–dependent apoptosis in human ovarian cancer cells. Phytother Res 29:1330–1338

Akperbekova B, Abdullaev R (1966) Diuretic effect of drug form and galenicals from the roots of *Cyperus rotundus* growing in Azerbaidzhan. IzvAkadNaukAzSsr Ser Biol Nauk 4:98

Al-Awar M, Alqabbani T (2021) Anti-diabetic, antioxidants, anti-hepatorenaltoxicity activities of *Cyperus rotundus* rhizome extract in alloxan-induced diabetic rats. Nat Volatiles Essent Oils 8:15115–15130

Al-Massarani S, Al-Enzi F, Al-Tamimi M, Al-Jomaiah N, Al-amri R, Başer KHC, Tabanca N, Estep AS, Becnel JJ, Bloomquist JR (2016) Composition & biological activity of *Cyperus rotundus* L. tuber volatiles from Saudi Arabia. Nat Volatiles Essent Oils 3:26–34

Al-Shammari AM, Abo-Altemen RA, Shawkat MS (2021) *Cyperus rotundus* L. alkaloid extracts enhance oncolytic Newcastle disease virus against digestive system neoplasms. S Afr J Bot 143:266–273

Al-Snafi AE (2016) A review on *Cyperus rotundus*: a potential medicinal plant. IOSR J Pharm 6:32–48

Babiaka SB, Moumbock AFA, Günther S, Ntie-Kang F (2021) Natural products in *Cyperus rotundus* L. (Cyperaceae): an update of the chemistry and pharmacological activities. RSC Adv 11:15060–15077

Badgujar SB, Bandivdekar AH (2015) Evaluation of a lactogenic activity of an aqueous extract of *Cyperus rotundus* Linn. J Ethnopharmacol 163:39–42

Baek J, Lee MG (2016) Oxidative stress and antioxidant strategies in dermatology. Redox Rep 21:164–169

Bai L, Li X, He L, Zheng Y, Lu H, Li J, Zhong L, Tong R, Jiang Z, Shi J, Li J (2019) Antidiabetic potential of flavonoids from traditional Chinese medicine: a review. Am J Chin Med 47:933–957

Bajpay A, Nainwal RC, Singh D, Tewari SK (2018) Medicinal value of *Cyperus rotundus* Linn: an updated review. Med Plants 10:165–170

Bezerra JJL, Pinheiro AAV (2022) Traditional uses, phytochemistry, and anticancer potential of *Cyperus rotundus* L. (Cyperaceae): a systematic review. S Afr J Bot 144:175–186

Biradar S, Kangralkar V, Mandavkar Y, Thakur M, Chougule N (2010) Anti-inflammatory, antiarthritic, analgesic and anticonvulsant activity of Cyperus essential oils. Int J Pharm Pharm Sci 2:112–115

Busman H, Nurcahyani N, Farisi S, Kanedi M, Prabiwi Dita M (2020) Inhibitory effects of tuber extract of nut grass (*Cyperus rotundus* L.) on the growth of rat fetuses. GSC Biol Pharm Sci 10:059–064

Cao M, Ou YL (2015) Study on the content of β-sitosterol in *Cyperus rotundus* from different origins. Shanxi Med J 44:1179–1180

Chang KS, Shin EH, Park C, Ahn YJ (2012) Contact and fumigant toxicity of *Cyperus rotundus* steam distillate constituents and related compounds to insecticide-susceptible and -resistant *Blattella germanica*. J Med Entomol 49:631–639

Chen Y, Zhao YY, Wang XT, Liu JT, Huang LQ, Peng CS (2011) GC-MS analysis and analgesic activity of essential oil from fresh rhizoma of *Cyperus rotundus*. J Chin Med Mater 34:1225–1229

Cheng CH, Chen YR, Ye QQ, Liang Y, He XR, Zhou ZL, Feng ZC (2014) A new isoflavonoid from the rhizomes of *Cyperus rotundus*. Asian J Chem 26:3967–3970

China Pharmacopoeia Committee (2020) Pharmacopoeia of the People's Republic of China. Part 1. China Medical Science and Technology Press, Beijing, pp. 270

Choi HJ, Lee JH, Jung YS (2014) (+)-Nootkatone inhibits tumor necrosis factor α/interferon γ-induced production of chemokines in HaCaT cells. Biochem Biophys Res Commun 447:278–284

Choi HJ, Chung TW, Park MJ, Jung YS, Lee SO, Kim KJ, Ha KT (2017) Water-extracted tubers of *Cyperus rotundus* L. enhance endometrial receptivity through leukemia inhibitory factor-mediated expression of integrin $\alpha V\beta 3$ and $\alpha V\beta 5$. J Ethnopharmacol 208:16–23

Dabaghian FH, Hashemi M, Entezari M, Movassaghi S, Goushegir SA, Kalantari S, Movafagh A, Sharifi ZN (2015) Effect of *Cyperus rotundus* on ischemia-induced brain damage and memory dysfunction in rats. Iran J Basic Med Sci 18:199–201

Dang GK, Parekar RR, Kamat SK, Scindia AM, Rege NN (2011) Anti-inflammatory activity of *Phyllanthus emblica*, *Plumbago zeylanica* and *Cyperus rotundus* in acute models of inflammation. Phytother Res 25:904–908

Daswani PG, Brijesh S, Tetali P, Birdi TJ (2011) Studies on the activity of *Cyperus rotundus* Linn. tubers against infectious diarrhea. Indian J Pharmacol 43:340–344

Deng YH, Liu YB, Luo SW, Li X, Deng JB (2012) Study on isolation of α-cyperone and its analgesic and antipyretic effects. Tradit Chin Drug Res Clin Pharmacol 23:620–623

Deng SR, Zhu XM, Wang X, Zhu J, Xia LB (2016) Study on determination of mesocyperusphenol A in fruit of *Cyperus rotundus* L. J Pharm Res 35:202–204

Deng S, Xia L, Zhu X, Zhu J, Cai M, Wang X (2019) Natural α-glucosidase inhibitors rapid fishing from *Cyperus rotundus* using immobilized enzyme affinity screening combined with UHPLC-QTOF-MS. Iran J Pharm Res 18:1508–1515

Duarte MC, Leme EE, Delarmelina C, Soares AA, Figueira GM, Sartoratto A (2007) Activity of essential oils from Brazilian medicinal plants on *Escherichia coli*. J Ethnopharmacol 111:197–201

Elezabeth V, Arumugam S (2014) GC-MS analysis of ethanol extract of *Cyperus rotundus* leaves. Int J Curr Biotechnol 2:19–23

El-Gohary H (2004) Study of essential oils of the tubers of *Cyperus rotundus* L. and *Cyperus alopecuroides* rottb. Bull Fac Pharm Cairo Univ 42:157–163

Elkaream G (2012) Role of *Cyperus rotundus* oil in decreasing hair growth. J Intercult Ethnopharmacol 1:111–118

Eltayeib AA, Ismaeel HU (2014) Extraction of *Cyperus rotundus* rhizomes oil, identification of chemical constituents and evaluation of antimicrobial activity of the oil in North Kordofan state. Int J Adv Res Chem Sci 1:18–29

Eröz Poyraz İ, Demirci B, Küçük S (2018) Volatiles of Turkish *Cyperus rotundus* L. roots. Rec Nat Prod 12:222–228

Essaidi I, Koubaier HBH, Snoussi A, Casabianca H, Chaabouni MM, Bouzouita N (2014) Chemical composition of *Cyperus rotundus* L. tubers essential oil from the south of Tunisia, antioxidant potentiality and antibacterial activity against foodborne pathogens. J Essent Oil Bear Plants 17:522–532

Fenanir F, Semmeq A, Benguerba Y, Badawi M, Dziurla MA, Amira S, Laouer H (2021) *In silico* investigations of some *Cyperus rotundus* compounds as potential anti-inflammatory inhibitors of 5-LO and LTA4H enzymes. J Biomol Struct Dyn 40:11571–11586

Feng YF, Guo XL, Meng Q, Gao Y, Li WM (2006) Study on the chemical substrates of SFE extract from *Rhizoma Cyperi*. Chin Tradit Herb Drugs 29:232–235

Ghannadi A, Rabbani M, Ghaemmaghami L, Malekian N (2012) Phytochemical screening and essential oil analysis of one of the Persian sedges; *Cyperus rotundus* L. Int J Pharm Sci Res 3:424–427

Gupta D, Singh V, Agrawal N (2016) Volatile constituents and antimicrobial activities of dried rhizome of *Cyperus rotundus* Linn. Int J Curr Microbiol Appl Sci 5:334–339

Ha JH, Lee KY, Choi HC, Cho J, Kang BS, Lim JC, Lee DU (2002) Modulation of radioligand binding to the GABAA-benzodiazepine receptor complex by a new component from *Cyperus rotundus*. Biol Pharm Bull 25:128–130

Hao GF, Tang MQ, Wei YJ, Che FY, Qian LJ (2017) Determination of antidepressant activity of *Cyperus rotundus* L. extract in rats. Trop J Pharm Res 16:867–871

He JC, Li XR, Yang LF (2015) Analysis of volatile constituents in herbal pair *Artemisiae argyi* folium-*Cyperi rhizoma* and its single herbs. Chin Med J Res Prac 29:37–40

He M, Yan P, Yang ZY, Zhang ZM, Yang TB, Hong L (2018) A modified multiscale peak alignment method combined with trilinear decomposition to study the volatile/heat-labile components in *Ligusticum chuanxiong* Hort-*Cyperus rotundus* rhizomes by HS-SPME-GC/MS. J Chromatogr B Analyt Technol Biomed Life Sci 1079:41–50

Hemanth Kumar K, Tamatam A, Pal A, Khanum F (2013) Neuroprotective effects of *Cyperus rotundus* on SIN-1 induced nitric oxide generation and protein nitration: ameliorative effect against apoptosis mediated neuronal cell damage. Neurotoxicology 34:150–159

Hemanth Kumar K, Razack S, Nallamuthu I, Khanum F (2014) Phytochemical analysis and biological properties of *Cyperus rotundus* L. Ind Crop Prod 52:815–826

Hendri B, Yanwirasti Y, Djong HT, Kanedi M (2016) Antiestrogenic effect of tuber extract of *Cyperus rotundus* L. on the endometrial thickness of mice (*Mus musculus* L.). World J Pharm Life Sci 2:341–347

Hendri B, Nuning N, Salman F, Mohammad K, Dita MP (2019) Inhibitory effects of tuber extract of Nut Grass (*Cyperus Rotundus* L.) on the growth of rat fetuses. Glob Acad J Pharm Drug Res 1:14–17

Hu LJ, Hu ZF, Guo HL, Jlin X, Zhao XJ (2012) Comparison of volatile oil components from four of *Cyperus rotundus* and health products of *Rhizoma Cyperi*. Chin J Exp Tradit Med Formulae 18:112–116

Hu QP, Cao XM, Hao DL, Zhang LL (2017) Chemical composition, antioxidant, DNA damage protective, cytotoxic and antibacterial activities of *Cyperus rotundus* rhizomes essential oil against foodborne pathogens. Sci Rep 7:45231

Huang B, He D, Chen G, Ran X, Guo W, Kan X, Wang W, Liu D, Fu S, Liu J (2018) α-Cyperone inhibits LPS-induced inflammation in BV-2 cells through activation of Akt/Nrf2/HO-1 and suppression of the NF-κB pathway. Food Funct 9:2735–2743

Hussein JS, Medhat D, Abdel-Latif Y, Morsy S, Gaafar AA, Ibrahim EA, Al-kashef AS, Nooman MU (2020) Amelioration of neurotoxicity induced by esfenvalerate: impact of *Cyperus rotundus* L. tuber extract. Comp Clin Path 30:1–10

Ibrahim SRM, Mohamed GA, Alshali KZ, Haidari RAA, El–kholy AA, Zayed MF (2018) Lipoxygenase inhibitors flavonoids from *Cyperus rotundus* aerial parts. Rev Bras Farmacogn 28:320–324

Imam MZ, Sumi CD (2014) Evaluation of antinociceptive activity of hydromethanol extract of *Cyperus rotundus* in mice. BMC Complement Altern Med 14:1–5

Ito T, Endo H, Shinohara H, Oyama M, Akao Y, Iinuma M (2012) Occurrence of stilbene oligomers in *Cyperus rhizomes*. Fitoterapia 83:1420–1429

Jaiswal Y, Liang Z, Guo P, Ho HM, Chen H, Zhao Z (2014) Tissue-specific metabolite profiling of *Cyperus rotundus* L. rhizomes and (+)-nootkatone quantitation by laser microdissection, ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry, and gas chromatography-mass spectrometry techniques. J Agric Food Chem 62:7302–7316

Janaki S, Zandi-Sohani N, Ramezani L, Szumny A (2018) Chemical composition and insecticidal efficacy of *Cyperus rotundus* essential oil against three stored product pests. Int Biodeterior Biodegrad 133:93–98

Jebasingh D, Devavaram Jackson D, Venkataraman S, Adeghate E, Starling Emerald B (2014) The protective effects of *Cyperus rotundus* on behavior and cognitive function in a rat model of hypoxia injury. Pharm Biol 52:1558–1569

Jeong SJ, Miyamoto T, Inagaki M, Kim YC, Higuchi R (2000) Rotundines A-C, three novel sesquiterpene alkaloids from *Cyperus rotundus*. J Nat Prod 63:673–675

Jia HM, Zou ZM (2014) Antidepressant effect evaluation of the ethanolic extract from the roots of *Cyperus rotundus* L. on cell membrane chromatography and different depression models. Eur J Integr Med 6:742

Jin J, Cai YL, Zhao ZX, Ruan JL (2006) Study on extraction technology and main components of volatile oil from *Cyperus rotundus*. J Chin Med Mater 29:490–492

Jin JH, Lee DU, Kim YS, Kim HP (2011) Anti–allergic activity of sesquiterpenes from the rhizomes of *Cyperus rotundus*. Arch Pharm Res 34:223–228

Jirovetz L, Wobus A, Buchbauer G, Shafi MP, Thampi PT (2004) Comparative analysis of the essential oil and SPME-headspace aroma compounds of *Cyperus rotundus* L. roots/tubers from south-India using GC, GC-MS and olfactometry. J Essent Oil Bear Plants 7:100–106

Jung SH, Kim SJ, Jun BG, Lee KT, Hong SP, Oh MS, Jang DS, Choi JH (2013) α-Cyperone, isolated from the rhizomes of *Cyperus rotundus*, inhibits LPS-induced COX-2 expression and PGE2 production through the negative regulation of NFκB signalling in RAW 264.7 cells. J Ethnopharmacol 147:208–214

Kabbashi AS, Mohammed SEA, Almagboul AZ, Ahmed IF (2015) Antimicrobial activity and cytotoxicity of ethanolic extract of *Cyperus rotundus* L. Am J Pharm Pharm Sci 2:1–13

Kabir H, Abbasi H (2018) Unani perspective and new researches of Sa'ad ku'fi (*Cyperus rotundus*): a review. J Drug Delivery Ther 8:378–381

Kabir I, Biswas S, Asaduzzaman M, Molla M, Rafe M (2019) Neurobehavioral activity study of methanolic whole plants extract of *Cyperus rotundus* Linn. J Pharm Negat Results 10:36–40

Kamala A, Middha SK, Karigar CS (2018) Plants in traditional medicine with special reference to *Cyperus rotundus* L.: a review. 3 Biotech 8:309

Kandikattu HK, Rachitha P, Krupashree K, Jayashree GV, Abhishek V, Khanum F (2015) LC-ESI-MS/MS analysis of total oligomeric flavonoid fraction of *Cyperus rotundus* and its antioxidant, macromolecule damage protective and antihemolytic effects. Pathophysiology 22:165–173

Kandikattu HK, Deep SN, Razack S, Amruta N, Prasad D, Khanum F (2017) Hypoxia induced cognitive impairment modulating activity of *Cyperus rotundus*. Physiol Behav 175:56–65

Kandikattu HK, Amruta N, Khanum F, Narayana V, Srinivasulu D (2021) A review on *Cyperus rotundus*: ancient weed to modern elixir of life phytochemistry and therapeutic uses of *Cyperus rotundus* (Mustaka). Pharm Biomed Res 7:221–250

Khalili M, Kiasalari Z, Roghani M, Azizi Y (2011) Anticonvulsant and antioxidant effect of hydro-alcoholic extract of *Cyperus rotundus* rhizome on pentylentetrazole-induced kindling model in male mice. J Med Plants Res 5:1140–1146

Khan S, Choi R-J, Lee D-U, Kim Y-S (2011) Sesquiterpene derivatives isolated from *Cyperus rotundus* L. inhibit inflammatory signaling mediated by NF-κB. Nat Prod Sci 17:250–255

Kilani S, Abdelwahed A, Ammar RB, Hayder N, Ghedira K, Chraief I, Hammami M, Chekir-Ghedira L (2005a) Chemical composition, antibacterial and antimutagenic activities of essential oil from (Tunisian) *Cyperus rotundus*. J Essent Oil Res 17:695–700

Kilani S, Ben Ammar R, Bouhlel I, Abdelwahed A, Hayder N, Mahmoud A, Ghedira K, Chekir-Ghedira L (2005b) Investigation of extracts from (Tunisian) *Cyperus rotundus* as antimutagens and radical scavengers. Environ Toxicol Pharmacol 20:478–484

Kilani S, Ben Sghaier M, Limem I, Bouhlel I, Boubaker J, Bhouri W, Skandrani I, Neffatti A, Ben Ammar R, Dijoux-Franca MG, Ghedira K, Chekir-Ghedira L (2008a) *In vitro* evaluation of antibacterial, antioxidant, cytotoxic and apoptotic activities of the tubers infusion and extracts of *Cyperus rotundus*. Bioresour Technol 99:9004–9008

Kilani S, Ledauphin J, Bouhlel I, Sghaier MB, Boubaker J, Skandrani I, Mosrati R, Ghedira K, Barillier D, Chekir-Ghedira L (2008b) Comparative study of *Cyperus rotundus* essential oil by a modified GC/MS analysis method. evaluation of its antioxidant, cytotoxic, and apoptotic effects. Chem Biodivers 5:729–742

Kilani-Jaziri S, Neffati A, Limem I, Boubaker J, Skandrani I, Sghair MB, Bouhlel I, Bhouri W, Mariotte AM, Ghedira K, Dijoux Franca MG, Chekir-Ghedira L (2009) Relationship correlation of antioxidant and antiproliferative capacity of *Cyperus rotundus* products towards K562 erythroleukemia cells. Chem Biol Interact 181:85–94

Kilani-Jaziri S, Bhouri W, Skandrani I, Limem I, Chekir-Ghedira L, Ghedira K (2011) Phytochemical, antimicrobial, antioxidant and antigenotoxic potentials of *Cyperus rotundus* extracts. S Afr J Bot 77:767–776

Kim SJ, Kim HJ, Kim HJ, Jang YP, Oh MS, Jang DS (2012) New patchoulane-type sesquiterpenes from the rhizomes of *Cyperus rotundus*. Bull Korean Chem Soc 33:3115–3118

Kim HG, Hong J, Huh Y, Park C, Hwang DS, Choi JH, Oh MS (2013) *Cyperi rhizoma* inhibits the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced reduction in nigrostriatal dopaminergenic neurons in estrogen–deprived mice. J Ethnopharmacol 148:322–328

Komai K, Tang CS (1989) A chemotype of *Cyperus rotundus* in Hawaii. Phytochemistry 28:1883–1886

Krisanapun C, Wongkrajang Y, Temsiririrkkul R, Kongsaktrakoon B, Peungvicha P (2012) Anti-diabetic effect and acute toxicity of the water extract of *Cyperus rotundus* L. in rats. FASEB J 26:686–688

Kubmarawa D, Ogunwande IA, Okorie DA, Olawore NO, Kasali AA (2005) Chemical constituents of the volatile oil of *Cyperus esculentus* L. from Nigeria. Flavour Frag J 20:640–641

Kumar KH, Khanum F (2013) Hydroalcoholic extract of *Cyperus rotundus* ameliorates H_2O_2-induced human neuronal cell damage via its anti–oxidative and anti–apoptotic machinery. Cell Mol Neurobiol 33:5–17

Kumar SS, Mishra S (2005) Hepatoprotective activity of rhizomes of *Cyperus rotundus* Linn against carbon tetrachloride-induced hepatotoxicity. Indian J Pharm Sci 67:84–88

Kumar M, Rani M, Meher B (2017) Review on pharmacology and phytochemistry of *Cyperus rotundus* L. Curr Res Pharm Sci 7:11–15

Kumar SB, Krishna S, Pradeep S, Mathews DE, Pattabiraman R, Murahari M, Murthy TPK (2021) Screening of natural compounds from *Cyperus rotundus* Linn against SARS-CoV-2 main protease (M(pro)): an integrated computational approach. Comput Biol Med 134:104524

Lawal OA, Oyedeji AO (2009) Chemical composition of the essential oils of *Cyperus rotundus* L. from South Africa. Molecules 14:2909–2917

Lee CH, Hwang DS, Kim HG, Oh H, Park H, Cho JH, Lee JM, Jang JB, Lee KS, Oh MS (2010) Protective effect of *Cyperi rhizoma* against 6–hydroxydopamine–induced neuronal damage. J Med Food 13:564–571

Lemaure B, Touche A, Zbinden I, Moulin J, Courtois D, Mace K, Darimont C (2007) Administration of *Cyperus rotundus* tubers extract prevents weight gain in obese Zucker rats. Phytother Res 21:724–730

Li ST (2013) Anaysis of volatile oil from rhizoma of *Cyperus rotundus* (Wen) by GC-MS. J Pharm Res 32:683–685

Li WM, Gao Y, Zeng JQ, Zhu HN, Jia JL (2000) Research on chemical constituents of supercritical extraction of *Cyperus rotundus*. Chin Tradit Herb Drugs 31:16–17

Lin XS, Wu HQ, Huang F, Huang XL (2006) Analysis of essential oils from *Cyperus rotundus* L. by GC–MS. J Chin Mass Spectrom Soc 27:40–44

Lin SQ, Zhou ZL, Zhang HL, Yin WQ (2015) Phenolic glycosides from the rhizomes of *Cyperus rotundus* and their antidepressant activity. J Korean Soc Appl Biol Chem 58:685–691

Lin SQ, Zhou ZL, Zhang HL, Yang HY, Ou YC (2017) Reaserch on extraction technology and chemical constituents of volatile oil from *Rhizoma Cyperi*. J Lingnan Norm Univ 38:52–62

Lin SQ, Zhou ZL, Li CY (2018) Cyprotuoside C and cyprotuoside D, two new cycloartane glycosides from the rhizomes of *Cyperus rotundus*. Chem Pharm Bull 66:96–100

Lin CH, Peng SF, Chueh FS, Cheng ZY, Kuo CL, Chung JG (2019) The ethanol crude extraction of *Cyperus rotundus* regulates apoptosis-associated gene expression in HeLa human cervical carcinoma cells *in vitro*. Anticancer Res 39:3697–3709

Liu P, Liu L, Tang YP, Duan JA, Yang NY (2010) A new cerebroside and its anti–proliferation effect on VSMCs from the radix of *Cyperus rotundus* L. Chin Chem Lett 21:606–609

Liu XC, Lu XN, Liu QZ, Liu ZL (2016) Chemical composition and insecticidal activity of the essential oil of *Cyperus rotundus* rhizomes against *Liposcelis bostrychophila* (Psocoptera: Liposcelididae). J Essent Oil Bear Plants 19:640–647

Lu J, Li W, Gao T, Wang S, Fu C, Wang S (2022) The association study of chemical compositions and their pharmacological effects of *Cyperi rhizoma* (Xiangfu), a potential traditional Chinese medicine for treating depression. J Ethnopharmacol 287:114962

Ma S, Wang F, Zhang C, Wang X, Wang X, Yu Z (2020) Cell metabolomics to study the function mechanism of *Cyperus rotundus* L. on triple–negative breast cancer cells. BMC Complement Med Ther 20:262

Majeed M, Nagabhushanam K, Bhat B, Ansari M, Pandey A, Bani S, Mundkur L (2022) The anti-obesity potential of *Cyperus rotundus* extract containing piceatannol, scirpusin A and scirpusin B from rhizomes: preclinical and clinical evaluations. Diabetes Metab Syndr Obes 15:369–382

Mannarreddy P, Denis M, Munireddy D, Pandurangan R, Thangavelu KP, Venkatesan K (2017) Cytotoxic effect of *Cyperus rotundus* rhizome extract on human cancer cell lines. Biomed Pharmacother 95:1375–1387

Mehdizadeh M, Hashem Dabaghian F, Shojaee A, Molavi N, Taslimi Z, Shabani R, Soleimani Asl S (2017) Protective effects of *Cyperus rotundus* extract on amyloid β–peptide (1–40)-induced memory impairment in male rats: a behavioral study. Basic Clin Neurosci 8:249–254

Moein K, Mohsen Y, Elahe T, Mehdi S, Behzad H, Shahbazi R (2018) Cell toxicity and inhibitory effects of *Cyperus rotundus* extract on *Streptococcus mutans*, *Aggregatibacter actinomycetemcomitans* and *Candida albicans*. Eur J Transl Myol 28:362–369

Mohamed GA (2015) Iridoids and other constituents from *Cyperus rotundus* L. rhizomes. Bull Fac Pharm (cairo Univ) 53:5–9

Mohamed AI, Beseni BK, Msomi NZ, Salau VF, Erukainure OL, Aljoundi A, Islam MSJJoBS, Dynamics (2021) The antioxidant and antidiabetic potentials of polyphenolic–rich extracts of *Cyperus rotundus* (Linn.). J Biomol Struct Dyn 28:1–13

Morimoto M, Komai K (2005) Plant growth inhibitors: patchoulane-type sesquiterpenes from *Cyperus rotundus* L. Weed Biol Manage 5:203–209

Nidugala H, Avadhani R, Prabhu A, Basavaiah R, Kumar K (2015) GC-MS characterization of *n*-hexane soluble compounds of *Cyperus rotundus* L. rhizomes. J Appl Pharm Sci 5:96–100

Oh GS, Yoon J, Lee GG, Kwak JH, Kim SW (2015) The hexane fraction of *Cyperus rotundus* prevents non-alcoholic fatty liver disease through the inhibition of liver X receptor α-mediated activation of sterol regulatory element binding protein-1c. Am J Chin Med 43:477–494

Okwu GN, Abanobi SE, Nnadi UV, Ujowundu CO, Ene AC (2015) Hypolipidemic properties of ethanol extract of *Cyperus rotundus* rhizome. Int J Biochem Res Rev 7:132–138

Ouattara B, Simard RE, Holley RA, Piette GJ-P, Bégin A (1997) Antibacterial activity of selected fatty acids and essential oils against six meat spoilage organisms. Int J Food Microbiol 37:155–162

Pal D, Dutta S, Sarkar A (2009) Evaluation of CNS activities of ethanol extract of roots and rhizomes of *Cyperus rotundus* in mice. Acta Pol Pharm 66:535–541

Park SE, Shin WT, Park C, Hong SH, Kim GY, Kim SO, Ryu CH, Hong SH, Choi YH (2014) Induction of apoptosis in MDA-MB-231 human breast carcinoma cells with an ethanol extract of *Cyperus rotundus* L. by activating caspases. Oncol Rep 32:2461–2470

Park YJ, Zheng H, Kwak JH, Chung KH (2019) Sesquiterpenes from *Cyperus rotundus* and 4α,5α–oxidoeudesm-11-en-3-one as a potential selective estrogen receptor modulator. Biomed Pharmacother 109:1313–1318

Parvez MK, Al–Dosari MS, Arbab AH, Niyazi S (2019) The *in vitro* and *in vivo* anti-hepatotoxic, anti-hepatitis B virus and hepatic CYP450 modulating potential of *Cyperus rotundus*. Saudi Pharm J 27:558–564

Pirzada AM, Ali HH, Naeem M, Latif M, Bukhari AH, Tanveer A (2015) *Cyperus rotundus* L.: traditional uses, phytochemistry, and pharmacological activities. J Ethnopharmacol 174:540–560

Priya Rani M, Padmakumari KP (2012) HPTLC and reverse phase HPLC methods for the simultaneous quantification and *in vitro* screening of antioxidant potential of isolated sesquiterpenoids from the rhizomes of *Cyperus rotundus*. J Chromatogr B Analyt Technol Biomed Life Sci 904:22–28

Puratchikody A, Devi C, Nagalakshmi G (2006) Wound healing activity of *Cyperus rotundus* linn. Indian J Pharm Sci 68:97

Qu HJ, Lin KW, Li XL, Ou HY, Tan YF, Wang M, Wei N (2021) Chemical constituents and anti-gastric ulcer activity of essential oils of *Alpinia officinarum* (Zingiberaceae), *Cyperus rotundus* (Cyperaceae), and their herbal pair. Chem Biodivers 18:2100214

Rabiei Z, Hojjati M, Rafieian-Kopaeia M, Alibabaei Z (2013) Effect of *Cyperus rotundus* tubers ethanolic extract on learning and memory in animal model of Alzheimer. Biomed Aging Pathol 3:185–191

Rajakrishnan R, Alfarhan AH, Al-Ansari AM, Lekshmi R, Sreelakshmi R, Benil PB, Kim YO, Tack JC, Na SW, Kim HJ (2020) Therapeutic efficacy of the root tubers of *Aconitum heterophyllum* and its substitute *Cyperus rotundus* in the amelioration of pylorus ligation induced ulcerogenic and oxidative damage in rats. Saudi J Biol Sci 27:1124–1129

Rao JC, Naidu B, Sarita P, Raju G (2019) Quantitative elemental analysis of *Cyperus rotundus* medicinal plant by PIXE and ICP-MS techniques. Indian J Pure Appl Phys 57:671–674

Rao Y, Li R, Wang XW, Xue BX, Li SW, Zhao Y, Zhang LH, Xu YT, Wu HH (2021) Data mining of compatibility characteristics for Chinese medicinal prescriptions containing *Nardostachyos radix et rhizoma*. Chin Tradit Herb Drugs 52:3331–3343

Raut NA, Gaikwad NJ (2006) Antidiabetic activity of hydroethanolic extract of *Cyperus rotundus* in alloxan induced diabetes in rats. Fitoterapia 77:585–588

Richa T, Suneet K (2014) Chemical constituents of the essential oil of *Cyperus rotundus* Linn. Int J Drug Dev Res 6:57–60

Rocha FG, Brandenburg MM, Pawloski PL, Soley BDS, Costa SCA, Meinerz CC, Baretta IP, Otuki MF, Cabrini DA (2020) Preclinical study of the topical anti–inflammatory activity of *Cyperus rotundus* L. extract (Cyperaceae) in models of skin inflammation. J Ethnopharmacol 254:112709

Ryu B, Kim HM, Lee JS, Cho YJ, Oh MS, Choi JH, Jang DS (2015) Sesquiterpenes from rhizomes of *Cyperus rotundus* with cytotoxic activities on human cancer cells *in vitro*. Helv Chim Acta 98:1372–1380

Saad Z, Mahmood N, Tawfeeq A, Yaseen N (2018) *Cyperus rotundus* tubers extract inhibits stem cell markers expression in cervical and human glioblastoma cancer cell lines. Iraqi J Med Sci 16:159–165

Sabir MN, Saour KY, Rachid S (2020) *In vitro* cytotoxic and antimicrobial effects of a novel peroxysesquiterpene glucoside from the rhizomes of *Cyperus rotundus* L. (Cyperaceae). Trop J Pharm Res 19:331–339

Samariya K, Sarin R (2013) Isolation and identification of flavonoids from *Cyperus rotundus* Linn. *in vivo* and *in vitro*. J Drug Delivery Ther 3:109–113

Samra RM, Soliman AF, Zaki AA, El–Gendy AN, Hassan MA, Zaghloul AM (2020) Chemical composition, antiviral and cytotoxic activities of essential oil from *Cyperus rotundus* growing in Egypt: evidence from chemometrics analysis. J Essent Oil Bear Plants 23:648–659

Samra RM, Soliman AF, Zaki AA, Ashour A, Al-Karmalawy AA, Hassan MA, Zaghloul AM (2021) Bioassay–guided isolation of a new cytotoxic ceramide from *Cyperus rotundus* L. S Afr J Bot 139:210–216

Sayed HM, Mohamed MH, Farag SF, Mohamed GA, Proksch P (2007) A new steroid glycoside and furochromones from *Cyperus rotundus* L. Nat Prod Res 21:343–350

Sayed HM, Mohamed MH, Farag SF, Mohamed GA, Omobuwajo OR, Proksch P (2008) Fructose-amino acid conjugate and other constituents from *Cyperus rotundus* L. Nat Prod Res 22:1487–1497

Seo WG, Pae HO, Oh GS, Chai KY, Kwon TO, Yun YG, Kim NY, Chung HT (2001) Inhibitory effects of methanol extract of *Cyperus rotundus* rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7 cells. J Ethnopharmacol 76:59–64

Seo Y-J, Yang Y-I, Jang D-S, Choi J-H (2014) Isocyperol isolated from rhizomes of *Cyperus rotundus*, inhibits iNOS and pro-inflammatory cytokines through suppressing STAT3 pathway in LPS-stimulated RAW264.7 cells. Cytokine 70:28–79

Shakerin Z, Esfandiari E, Razavi S, Alaei H, Ghanadian M, Dashti G (2020) Effects of *Cyperus rotundus* extract on spatial memory impairment and neuronal differentiation in rat model of Alzheimer's disease. Adv Biomed Res 9:1–7

Sharma A, Verma R, Ramteke P (2014) *Cyperus rotundus*: a potential novel source of therapeutic compound against urinary tract pathogens. J Herb Med 4:74–82

Sheng FY, Lu JR, Peng W, Fu CM, Zhang LL, Liu F, Wang SY (2013) Comparative study on GC-MS fingerprints of volatile oil in crude and processed *Cyperi rhizoma*. Chin Tradit Herb Drugs 44:3321–3327

Shi X, Wang X, Wang D, Geng Y, Liu J (2009) Separation and purification of α-cyperone from *Cyperus rotundus* with supercritical fluid extraction and high-speed counter-current chromatography. Sep Sci Technol 44:712–721

Shin JS, Hong Y, Lee HH, Ryu B, Cho YW, Kim NJ, Jang DS, Lee KT (2015) Fulgidic acid isolated from the rhizomes of *Cyperus rotundus* suppresses LPS-induced iNOS, COX-2, TNF-α, and IL-6 expression by AP-1 inactivation in RAW264. 7 macrophages. Biol Pharm Bull 38:1081–1086

Shivakumar S, Suresh H, Hallikeri C, Hatapakki B, Handiganur J, Sankh K, Shivakumar B (2009) Anticonvulsant effect of *Cyperus rotundus* Linn rhizomes in rats. J Nat Rem 9:192–196

Sim Y, Choi JG, Gu PS, Ryu B, Kim JH, Kang I, Jang DS, Oh MS (2016) Identification of neuroactive constituents of the ethyl acetate fraction from *Cyperi rhizoma* using bioactivity-guided fractionation. Biomol Ther 24:438–445

Simorangkir D, Masfria M, Harahap U, Satria D (2019) Activity anticancer *n*-hexane fraction of *Cyperus rotundus* L. rhizome to breast cancer MCF-7 cell line. Open Access Maced J Med Sci 7:3904–3906

Singh SP, Raghavendra K, Dash AP (2009) Evaluation of hexane extract of tuber of root of *Cyperus rotundus* Linn (Cyperaceae) for repellency against mosquito vectors. J Parasitol Res 2009:1–5

Singh P, Khosa RL, Mishra G, Jha KK (2015) Antidiabetic activity of ethanolic extract of *Cyperus rotundus* rhizomes in streptozotocin-induced diabetic mice. J Pharm BioAllied Sci 7:289–292

Sivapalan SR (2013) Medicinal uses and pharmacological activities of *Cyperus rotundus* Linn-a review. Int Sci Res Publ 3:1–8

Song BW, Zhang FJ, Liu JQ, Yang Y, Fu Z (2016) Study on the anti-hepatpma activity of *Cyperus Rotundus* by supercritical CO_2 fluid extraction *in vitro*. J Zhejiang Univ Technol 44:645–648

Sonwa MM, König WA (2001) Chemical study of the essential oil of *Cyperus rotundus*. Phytochemistry 58:799–810

Soumaya KJ, Dhekra M, Fadwa C, Zied G, Ilef L, Kamel G, Leila CG (2013) Pharmacological, antioxidant, genotoxic studies and modulation of rat splenocyte functions by *Cyperus rotundus* extracts. BMC Complement Altern Med 13:1–11

Soumaya KJ, Zied G, Nouha N, Mounira K, Kamel G, Geniève FDM, Leila GC (2014) Evaluation of *in vitro* antioxidant and apoptotic activities of *Cyperus rotundus*. Asian Pac J Trop Med 7:105–112

Sripanidkulchai B, Wongpanich V, Laupattarakasem P, Suwansaksri J, Jirakulsomchok D (2001) Diuretic effects of selected Thai indigenous medicinal plants in rats. J Ethnopharmacol 75:185–190

Srivastava RK, Singh A, Shukla SV (2013) Chemical investigation and pharmaceutical action of *Cyperus rotundus*-a review. J Biol Act Prod Nat 3:166–172

Susianti S, Yanwirasti Y, Darwin E (2018) The cytotoxic effects of purple nutsedge (*Cyperus rotundus* L.) tuber essential oil on the HeLa cervical cancer cell line. Pak J Biotechnol 15:77–81

Sutalangka C, Wattanathorn J (2017) Neuroprotective and cognitive-enhancing effects of the combined extract of *Cyperus rotundus* and *Zingiber officinale*. BMC Complement Altern Med 17:135

Taheri Y, Herrera-Bravo J, Huala L, Salazar LA, Sharifi-Rad J, Akram M, Shahzad K, Melgar-Lalanne G, Baghalpour N, Tamimi K, Mahroo-Bakhtiyari J, Kregiel D, Dey A, Kumar M, Suleria HAR, Cruz-Martins N, Cho WC (2021) *Cyperus* spp.: a review on phytochemical composition, biological activity, and health-promoting effects. Oxid Med Cell Longev 2021:4014867

Tam CU, Yang FQ, Zhang QW, Guan J, Li SP (2007) Optimization and comparison of three methods for extraction of volatile compounds from *Cyperus rotundus* evaluated by gas chromatography-mass spectrometry. J Pharm Biomed Anal 44:444–449

Thanabhorn S, Jaijoy K, Thamaree S, Ingkaninan K, Panthong A (2005) Acute and subacute toxicities of the ethanol extract from the rhizomes of *Cyperus rotundus* Linn. Mahidol Univ J Pharm Sci 32:15–22

Thebtaranonth C, Thebtaranonth Y, Wanauppathamkul S, Yuthavong Y (1995) Antimalarial sesquiterpenes from tubers of *Cyperus rotundus*: structure of 10, 12-peroxycalamenene, a sesquiterpene endoperoxide. Phytochemistry 40:125–128

Thomas D, Govindhan S, Baiju EC, Padmavathi G, Kunnumakkara AB, Padikkala J (2015) *Cyperus rotundus* L. prevents non-steroidal anti-inflammatory drug-induced gastric mucosal damage by inhibiting oxidative stress. J Basic Clin Physiol Pharmacol 26:485–490

Tsoyi K, Jang HJ, Lee YS, Kim YM, Kim HJ, Seo HG, Lee JH, Kwak JH, Lee DU, Chang KC (2011) (+)-Nootkatone and (+)-valencene from rhizomes of *Cyperus rotundus* increase survival rates in septic mice due to heme oxygenase–1 induction. J Ethnopharmacol 137:1311–1317

Uddin SJ, Mondal K, Shilpi JA, Rahman MT (2006) Antidiarrhoeal activity of *Cyperus rotundus*. Fitoterapia 77:134–136

Visetson S, Milne M, John M (2001) Toxicity of 4,11-selinnadien-3-one from nutsedge (*Cyperus rotundus* L.) tuber extracts to diamondback moth larvae (*Plutella xylostella* L.), detoxification mechanisms and toxicity to non target species. Kasetsart J 35:284–292

Wang M, Yang TT, Rao Y, Wang ZM, Dong X, Zhang LH, Han L, Zhang Y, Wang T, Zhu Y, Gao XM, Li TX, Wang HY, Xu YT, Wu HH (2021a) A review on traditional uses, phytochemistry, pharmacology, toxicology and the analytical methods of the genus *Nardostachys*. J Ethnopharmacol 280:114–144

Wang Q, Lou JH, Zhao ZY, Duan WL, Wang JH, Zeng GZ, Yin JL (2021b) Cyperensol A, a novel sesquiterpenoid with a unique 6/6/5 skeleton from *Cyperus rotundus* L. Tetrahedron Lett 87:153543

Wang F, Song X, Ma S, Liu C, Sun X, Wang X, Liu Z, Liang D, Yu Z (2019) The treatment role of *Cyperus rotundus* L. to triple-negative breast cancer cells. Biosci Rep 39

Weenen H, Nkunya M, Bray D, Mwasumbi L, Kinabo L, Kilimali V, Wijnberg J (1990a) Antimalarial compounds containing an α, β–unsaturated carbonyl moiety from Tanzanian medicinal plants. Planta Med 56:371–373

Weenen H, Nkunya MH, Bray D, Mwasumbi LB, Kinabo LS, Kilimali V (1990b) Antimalarial activity of Tanzanian medicinal plants. Planta Med 56:368–370

Wu X (2007) The research on the chemical constituents from the bioactivity part and on the raw material quality specification of *Rhizoma Cyperi*. Chengdu University of Traditional Chinese Medicine, Chengdu (China), pp 21

Xu QJ, Wang Y, Li L, Hao XY (2006) A comparison of chemical constituents of volatile oil extracted from processed and unprocessed Cyperus. Guiyang Yixueyuan Xuebao 31:413–415

Xu Y, Zhang HW, Yu CY, Lu Y, Chang Y, Zou ZM (2008) Norcyperone, a novel skeleton norsesquiterpene from *Cyperus rotundus* L. Molecules 13:2474–2481

Xu HB, Ma YB, Huang XY, Geng CA, Wang H, Zhao Y, Yang TH, Chen XL, Yang CY, Zhang XM, Chen JJ (2015) Bioactivity–guided isolation of anti-hepatitis B virus active sesquiterpenoids from the traditional Chinese medicine: rhizomes of *Cyperus rotundus*. J Ethnopharmacol 171:131–140

Xue N, Guo HB, Ma HX, Miao MS, Zhu PS (2022) Study on characteristics of traditional Chinese medicine in treatment of pepticulcer based on data mining. Chin Tradit Herb Drugs 53:799–805

Yadav R, Mani M, Kaur R (2022) A comprehensive review on anti-obesity potential of *Cyperus rotundus* in experimental animals. Ymer 21:144–153

Yagi S, Babiker R, Tzanova T, Schohn H (2016) Chemical composition, antiproliferative, antioxidant and antibacterial activities of essential oils from aromatic plants growing in Sudan. Asian Pac J Trop Med 9:763–770

Yang JL, Shi YP (2012) Structurally diverse terpenoids from the rhizomes of *Cyperus rotundus* L. Planta Med 78:59–64

Ying J, Bing X (2016) Chemical constituents of *Cyperus rotundus* L. and their inhibitory effects on uterine fibroids. Afr Health Sci 16:1000–1006

Yu HH, Lee DH, Seo SJ, You YO (2007) Anticariogenic properties of the extract of *Cyperus rotundus*. Am J Chin Med 35:497–505

Yulianty FS, Sutyarso BH (2019) Regulation of integrin $\beta 3$ protein secretion on implantation embryo of mouse (*Mus musculus* L.) induced by oil atsiri of *Purple nutsedge* Tubers (*Cyperus rotundus* L.). Annu Res Rev Biol 33:1–5

Zhang T, Xu L, Xiao H, Zhou X, Mo S, Cai S, Zhou Z (2014) A new iridoid glycoside from the rhizomes of *Cyperus rotundus*. Bull Korean Chem Soc 35:2207–2209

Zhang LL, Zhang LF, Hu QP, Hao DL, Xu JG (2017) Chemical composition, antibacterial activity of *Cyperus rotundus* rhizomes essential oil against *Staphylococcus aureus* via membrane disruption and apoptosis pathway. Food Control 80:290–296

Zhao XH, Su SL, Duan JA, Liu TS, Hou PF, Shang EX, Tang YP (2008) Rearch on quality correlation analysis of *Rhizoma Cyperi*. Chin J Pharm Anal 28:187–192

Zhou Z, Fu C (2013) A new flavanone and other constituents from the rhizomes of *Cyperus rotundus* and their antioxidant activities. Chem Nat Compd 48:963–965

Zhou Z, Yin W (2012) Two novel phenolic compounds from the rhizomes of *Cyperus rotundus* L. Molecules 17:12636–12641

Zhou Z, Zhang H (2013) Phenolic and iridoid glycosides from the rhizomes of *Cyperus rotundus* L. Med Chem Res 22:4830–4835

Zhou Z, Yin W, Zhang H, Feng Z, Xia J (2013) A new iridoid glycoside and potential MRB inhibitory activity of isolated compounds from the rhizomes of *Cyperus rotundus* L. Nat Prod Res 27:1732–1736

Zhou ZL, Yin WQ, Yang YM, He CH, Li XN, Zhou CP, Guo H (2016a) New iridoid glycosides with antidepressant activity isolated from *Cyperus rotundus*. Chem Pharm Bull 64:73–77

Zhou ZL, Lin SQ, Yin WQ (2016b) New cycloartane glycosides from the rhizomes of *Cyperus rotundus* and their antidepressant activity. J Asian Nat Prod Res 18:662–668

Zhu M, Luk H, Fung H, Luk C (1997) Cytoprotective effects of *Cyperus rotundus* against ethanol induced gastric ulceration in rats. Phytother Res 11:392–394

Zoghbi MdGB, Andrade EHA, Carreira LMM, Rocha EAS (2008) Comparison of the main components of the essential oils of "priprioca": *Cyperus articulatus* var. *articulatus* L., *C. articulatus* var. *nodosus* L., *C. prolixus* Kunth and *C. rotundus* L. J Essent Oil Res 20:42–45