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Review

Chemical Composition and Anticancer Activity of Essential Oils from Cyperaceae Species: A Comprehensive Review

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Abstract: Cancer is one of the leading causes of mortality worldwide, and the currently available therapies are often associated with severe side effects, including nephrotoxicity, hepatotoxicity, and cardiotoxicity. In this context, essential oils (EOs) have stood out as a less toxic natural alternative, with their anticancer potential widely investigated in in vitro and in vivo studies. The present study aimed to review, for the first time, the chemical composition, anticancer potential, and biological safety of EOs extracted from species of the Cyperaceae family. Research was conducted in different databases, covering publications from the first report on the topic in 1989 to November 2024. This review highlights 33 Cyperaceae species known to produce essential oils, with sesquiterpenes (67%) identified as the predominant compounds. The notable compounds across multiple species include cyperene, cyperotundone, caryophyllene oxide, and mustakone. Regarding the pharmacological potential, the EOs of *Cyperus rotundus*, *Cyperus kyllingia*, and *Cyperus longus* exhibited high cytotoxic activity against the HCT-116, HepG2, MCF-7, HeLa, and NCI-H187 cell lines. The mechanisms of action associated with the anticancer effect of EOs include DNA fragmentation, cell cycle arrest, and induction of apoptosis. Acute toxicity reports indicate that only the EOs of *Cyperus articulatus* have been evaluated in rodents and deemed biologically safe.

Keywords: *Cyperus rotundus*; sesquiterpenes; cytotoxicity; antitumor; antiproliferative

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1. Introduction

Cancer is one of the leading causes of global mortality, with projections indicating that the annual number of new cases could reach 35 million by 2050, an increase of 77% compared to 2022 [1,2]. The continued increase in global cancer incidence is attributed to population aging, population growth, and risk factors such as smoking, obesity, and physical inactivity [3].

Despite therapeutic advances, many patients, especially in low- and middle-income countries, struggle to access anticancer therapies due to delays in global rollout or local unavailability [4]. Furthermore, while effective, the existing therapies are often associated with severe side effects, such as nephrotoxicity, hepatotoxicity, and cardiotoxicity [5–8]. In this scenario, natural products emerge as promising alternatives to support cancer treatment, offering therapeutic potential with lower toxicity [9–13]. Essential oils (EOs), volatile compounds present in several species, have aroused great interest due to their anticancer potential demonstrated in in vitro and in vivo studies [14–16].

Species from the Cyperaceae family, including *Cyperus kyllingia* Endl. [17], *Cyperus amuricus* Maxim. [18], and *Cyperus rotundus* L. [19], are traditionally used in in India,

Bangladesh, and Philippines for the treatment of cancer. These ethnomedicinal applications have been scientifically validated, with EOs from *C. rotundus* [20] and *C. kyllingia* [21] demonstrating significant cytotoxic activity against colon cancer (HCT-116), breast cancer (MCF-7), hepatocellular carcinoma (HepG2), and lung carcinoma (NCI-H187) cell lines. Chemically, the EO of *C. rotundus* is rich in sesquiterpenes, with an emphasis on cyperotundone, cyperene, and caryophyllene oxide [22–25]. When evaluated in isolation, these compounds exhibited cytotoxic potential against different cancer cell lines [26–28].

Based on this evidence and the need to develop less aggressive therapeutic alternatives for cancer treatment, this study reviewed, for the first time, the chemical composition, anticancer potential, and biological safety of EOs obtained from Cyperaceae species.

2. Methodology

2.1. Databases

Documents were retrieved from the following databases: Google Scholar (https://scholar.google.com/ (accessed on 1 November 2024)), PubMed® (https://pubmed.ncbi.nlm.nih.gov/ (accessed on 1 November 2024)), SciELO (https://search.scielo.org/ (accessed on 1 November 2024)), SpringerLink® (https://link.springer.com/ (accessed on 1 November 2024)), Scopus® (http://www.scopus.com/ (accessed on 1 November 2024)), and Web of Science™ (https://www.webofknowledge.com (accessed on 1 November 2024)). The keywords used for this research were as follows: "anticancer AND essential oil AND Cyperaceae", "cytotoxicity AND essential oil AND Cyperaceae", "antiproliferative AND essential oil AND Cyperaceae", "antitumor AND essential oil AND Cyperaceae", "phytochemistry AND essential oil AND Cyperaceae", and "toxicity AND essential oil AND Cyperaceae".

2.2. Inclusion and Exclusion Criteria

Articles that presented specific information on the chemical composition of EOs from Cyperaceae species were selected, covering publications from the first report by Komai and Tang [29] to November 2024. Studies that addressed the anticancer, antitumor, antiproliferative, cytotoxic potential, and acute oral toxicity in vivo of these oils were also included. Review articles, e-books, book chapters, undergraduate theses, masters' thesis, Ph.D. thesis, and works published in technical or scientific events were excluded. Furthermore, studies that did not provide detailed information on the extraction methods and analytical techniques used to characterize the chemical composition of EOs, as well as those that mentioned species only at the genus level, were discarded [30]. The scientific names of the species were verified on the website World Flora Online (WFO) Plant List (https://wfoplantlist.org/, (accessed on 1 November 2024)).

2.3. Selection of Scientific Documents and Categorization of Information

Initially, 90 scientific articles were identified in the consulted databases (Figure 1). After applying the inclusion and exclusion criteria, 24 documents were eliminated. Thus, 66 articles that provided data on the chemical composition, anticancer potential, and toxicity of EOs from Cyperaceae species were included in this review. The results were organized into three main categories: (1) chemical composition of essential oils from Cyperaceae species; (2) anticancer activity of essential oils from Cyperaceae species; and (3) acute oral toxicity of essential oils from Cyperaceae species.

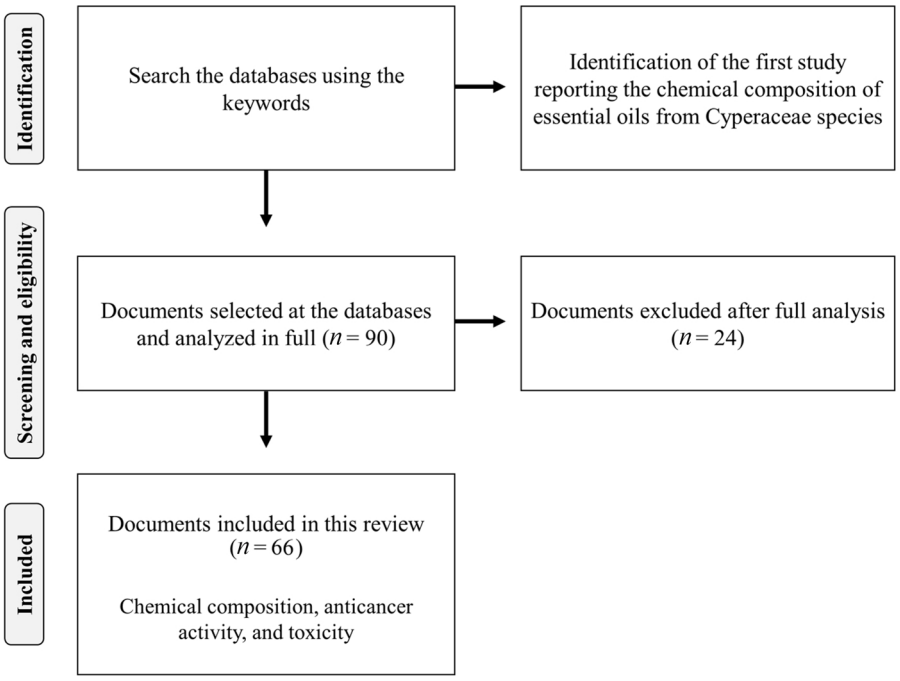

Figure 1. Flow diagram of selection of scientific documents included in this review.

2.4. Data Analysis

The results of studies on the in vitro anticancer activity of EOs from Cyperaceae species were analyzed based on the criteria of the U.S. National Cancer Institute—NCI [31] and Niksic et al. [32]. According to these parameters, EOs that exhibited IC_{50} values (concentration required to reduce cell viability by 50%) equal to or lower than 20 µg/mL against different cancer cell lines were classified as highly cytotoxic.

3. Results and Discussion

The *Cyperus* genus was the most investigated in relation to the chemical composition of its EOs, covering a total of 23 species, with an emphasis on *C. rotundus* and *C. articulatus* L. Furthermore, studies were found for representatives of the genera *Carex* (2 spp.), *Eleocharis* (2 spp.), *Scleria* (2 spp.), *Blysmus* (1 sp.), *Fimbristylis* (1 sp.), *Rhynchospora* (1 sp.), and *Schoenoplectus* (1 sp.) (Table 1).

Table 1. Chemical composition of essential oils from Cyperaceae species [1].

Genus/Species	Part of the Plant	Extraction Method	Major Compounds	Chemical Class	References
Blysmus					
Blysmus rufus (Huds.) Link (Syn. *Scirpus littoralis* Schrad.)	Aerial parts	Hydrodistillation	Cyperene (18.7%), cyperotundone (14.8%)	Sesquiterpene	[33]
Carex					
Carex meyeriana Kunth	Aerial parts	Hydrodistillation	Palmitic acid (43.06%), linolenic acid (28.46%)	Saturated fatty acid, essential fatty acid	[34]
Carex pseudofoetida Kük.	Aerial parts	Hydrodistillation	Cyperene (31.5%), cyperotundone (13.5%)	Sesquiterpene	[35]

Table 1. *Cont.*

Genus/Species	Part of the Plant	Extraction Method	Major Compounds	Chemical Class	References
Cyperus					
Cyperus arenarius Retz.	Aerial parts	Hydrodistillation	Cyperene (21.9%), cyperotundone (12.5%)	Sesquiterpene	[36]
Cyperus articulatus L.	Rhizomes	Hydrodistillation	Cyperotundone (42.3%), piperitone (10.1%), β-maaliene (8.4%)	Sesquiterpene, monoterpene	[37]
	Stems, rhizomes	Hydrodistillation	Caryophyllene oxide (4.6–27.4%), mustakone (7.3–14.5%), α-pinene (0.7–12.9%)	Sesquiterpene, monoterpene	[38]
	Rhizomes	Hydrodistillation	Cyperene (33.5%), β-santalene (5.5%)	Sesquiterpene	[39]
	Tubers, aerial parts	Hydrodistillation	Caryophyllene oxide (16.63–18.22%), γ-patchoulene (12.07–12.79%)	Sesquiterpene	[40]
	Underground parts	Hydrodistillation	α-Cadinol (12.07%), *trans*-pinocarveol (9.86%), cyperenone (7.28%)	Sesquiterpene, monoterpene	[41]
	Underground parts	Hydrodistillation	α-Pinene (10.09%), mustakone (8.27%), *trans*-pinocarveol (7.45%)	Monoterpene, sesquiterpene	[42]
	Rhizomes	Steam distillation	Mustakone (9.9%), cyclocolorenone (7.4%)	Sesquiterpene	[43]
	Rhizomes	Hydrodistillation	Mustakone (251.0 mg/g of dried rhizomes), cyperotundone (97.0 mg/g of dried rhizomes)	Sesquiterpene	[44]
	Rhizomes	Hydrodistillation	Mustakone (11.6%), cyclocolorenone (10.3%), α-pinene (8.26%)	Sesquiterpene, monoterpene	[45]
	Rhizomes	Hydrodistillation	Mustakone (20.2%), longifolenaldehyde (14.9%)	Sesquiterpene	[46]
	Rhizomes	Hydrodistillation	Mustakone (21.4%), eudesma-4(15)-7-dien-1β-ol (8.8%)	Sesquiterpene	[25]
	Rhizomes	Hydrodistillation	Mustakone (10.65%), β-selinene (8.45%)	Sesquiterpene	[47]
Cyperus brevifolius (Rottb.) Hassk. (Syn. *Kyllinga brevifolia* Rottb.)	Roots, rhizomes	*n*-Hexane extraction	δ-Cadinene (9.5%), α-humulene (7.8%), β-elemene (7.3%)	Sesquiterpene	[29]
	Aerial parts, rhizomes	Hydrodistillation	Manoyl oxide (6.8–31.1%), 13-epi-manoyl oxide (5.7–26.1%), 11α-hydroxymanoyl oxide (5.9–16.2%), 1β-hydroxymanoyl oxide (4.6–22.1%)	Diterpene	[48]
	Leaves	Hydrodistillation	α-Cadinol (40.3 %), τ-muurolol (19.5 %), germacrene D-4-ol (12.5 %)	Sesquiterpene	[49]
	Underground parts	Hydrodistillation	Manoyl oxide (44.08%), β-pinene (13.58%), cyperene (7.63%)	Diterpene, monoterpene, sesquiterpene	[41]
Cyperus capitatus Vand.	Aerial parts	Hydrodistillation	Cyperene (42.93%), cyperotundone (10.66%)	Sesquiterpene	[50]

Table 1. *Cont.*

Genus/Species	Part of the Plant	Extraction Method	Major Compounds	Chemical Class	References
Cyperus compressus L.	Roots	Hydrodistillation	Caryophyllene oxide (34.0%), cyperene (25.6%)	Sesquiterpene	[51]
Cyperus conglomeratus Rottb.	Aerial parts	Hydrodistillation	Cyperene (27.2%), cyperol (8.7%), cyperotundone (8.1%)	Sesquiterpene	[52]
	Rhizomes	Hydrodistillation	Eugenol (31.3%), α-cyperone (10.5%), cyperotundone (8.4%)	Phenolic compound, sesquiterpene	[53]
Cyperus difformis L.	Aerial parts	Hydrodistillation	Cyperene (34.8%), cyperotundone (7.8%), isorotundene (7.8%)	Sesquiterpene	[36]
	Aerial parts	Hydrodistillation	Cyperene (44.31%), cyperotundone (11.57%)	Sesquiterpene	[50]
Cyperus distans L.f.	Rhizomes	Hydrodistillation	Cyperene (47.6%), α-pinene (18.8%), 1,8-cineole (14.5%), caryophyllene oxide (7.3%)	Sesquiterpene, monoterpene	[54]
	Rhizomes	Hydrodistillation	Zierone (33.9%), caryophyllene oxide (14.2%), α-cyperone (9.0%)	Sesquiterpene	[55]
Cyperus erectus (Schumach.) Mattf. & Kük. (Syn. *Kyllinga erecta* Schumach.)	Rhizomes	Hydrodistillation	Manoyl oxide (48.0%), cyperotundone (10.2%)	Diterpene, sesquiterpene	[56]
	Aerial parts	Hydrodistillation	1,8-Cineole (10.5%), α-humulene (21.7%), farnesyl acetate (11.2%), β-caryophyllene (9.9%)	Monoterpene, sesquiterpene	[57]
Cyperus esculentus L.	Tubers	Hydrodistillation	α-Pinene (70.5–75.5%), α-thujene (5.2–10.2%)	Monoterpene	[58]
	Tubers, aerial parts	Hydrodistillation	Cyperene (23.06%), caryophyllene oxide (19.41%), γ-patchoulene (13.11%)	Sesquiterpene	[40]
Cyperus fuscus L.	Burrs	Hydrodistillation	Dehydroaromadendrene (10.7%), α-selinene (7.5%)	Sesquiterpene	[59]
Cyperus giganteus Vahl	Rhizomes	Hydrodistillation	Cyperotundone (30.4%), cyperene (10.4%)	Sesquiterpene	[60]
Cyperus glomeratus L.	Underground parts	Hydrodistillation	Caryophyllene oxide (44.8%), humulene epoxide II (14.1%), β-caryophyllene (12.6%), α-humulene (7.8%)	Sesquiterpene	[61]
Cyperus hortensis (Salzm. ex Steud.) Dorr (Syn. *Kyllinga pumila* Michx.)	Leaves	Hydrodistillation	β-Elemene (12.5%), *Z*-caryophyllene (11.3%), germacrene D (7.1%)	Sesquiterpene	[62]
Cyperus laevigatus L.	Aerial parts	Hydrodistillation	Hexahydrofarnesyl acetone (19.13%), (Z)-myroxide (8.14%), phytol (6.96%), limonene (6.74%)	Sesquiterpene, monoterpene, diterpene	[63]
Cyperus longus L.	Aerial parts	Steam distillation	β-Himachalene (46.6%), α-humulene (16.7%), γ-himachalene (10.1%)	Sesquiterpene	[64]
	Whole plant	Hydrodistillation	β-Himachalene (10.81%), α-caryophyllene oxide (7.6%), aristolone (6.39%)	Sesquiterpene	[65]

Table 1. *Cont.*

Genus/Species	Part of the Plant	Extraction Method	Major Compounds	Chemical Class	References
Cyperus maculatus Boeckeler	Rhizomes	Steam distillation	Mustakone (22.0%), α-copaene (8.2%), cyperene (7.8%)	Sesquiterpene	[66]
Cyperus papyrus L.	Tubers, aerial parts	Hydrodistillation	Cyperene (18.32%), copaene (8.83%)	Sesquiterpene	[40]
	Rhizomes	Hydrodistillation	Caryophyllene oxide (12.7%), cyperene (10.2%), 1,8-cineole (8.4%)	Sesquiterpene, monoterpene	[67]
Cyperus pedunculatus (R.Br.) J.Kern (Syn. *Remirea maritima* Aubl.)	Roots, rhizomes	Hydrodistillation	Remirol (43.2%), cyperene (13.8%)	Benzenoid, sesquiterpene	[68]
Cyperus prolixus Kunth	Tubers	Hydrodistillation	Caryophyllene oxide (6.9–26.8%), α-cyperone (13.5–20.6%)	Sesquiterpene	[69]
Cyperus rotundus L.	Roots, tubers	Steam distillation	α-Copaene (11.4%), valerenal (9.8%), caryophyllene oxide (9.7%), cyperene (8.4%)	Sesquiterpene	[70]
	Tubers	Hydrodistillation	Cyperene (30.9%), cyperotundone (8.8%)	Sesquiterpene	[71]
	Tubers	Hydrodistillation	α-Cyperone (25.23%), cyperene (20.38%)	Sesquiterpene	[72]
	Rhizomes	Hydrodistillation	β-Pinene (11.3%), α-cyperone (11.0%), α-pinene (10.8%), myrtenol (7.9%)	Monoterpene, sesquiterpene	[73]
	Tubers	Hydrodistillation	Cyperene (16.9%), caryophyllene oxide (8.9%), α-longipinane (8.4%)	Sesquiterpene	[22]
	Aerial parts	Hydrodistillation	Cyperotundone (11.2%), isorotundene (9.5%), cyperol (6.4%)	Sesquiterpene	[23]
	Tubers	Hydrodistillation	Cyperotundone (19.7%), cyperene (15.2%)	Sesquiterpene	[24]
	Tubers	Hydrodistillation	α-Cyperone (21.1%), 4-oxo-α-ylangene (12.8%)	Sesquiterpene	[20]
	Rhizomes	Steam distillation	α-Cyperone (29.38%), cyperene (13.97%)	Sesquiterpene	[74]
	Rhizomes	Hydrodistillation	2,5,9-trimethylcycloundeca-4,8-dienone (13.44%), alloaromadendrene oxide-(1) (8.47%), piperitone (7.37%), β-elemol (7.14%),	Sesquiterpene, monoterpene	[75]
	Rhizomes	Hydrodistillation	α-Cyperone (38.46%), cyperene (12.84%), α-selinene (11.66%)	Sesquiterpene	[76]
	Rhizomes	Hydrodistillation	α-Cyperone (38.46%), cyperene (12.84%), α-selinene (11.66%)	Sesquiterpene	[77]
	Rhizomes	Hydrodistillation	Elemenone (13.59%), α-cyperone (13.14%), caryophyllene oxide (13.03%)	Sesquiterpene	[78]
	Rhizomes	Hydrodistillation	Humulene epoxide (38.43%), caryophyllene oxide (21.03%)	Sesquiterpene	[79]
	Rhizomes	Hydrodistillation	Longiverbenone (18.53%), cyperotundone (12.75%)	Sesquiterpene	[80]

Table 1. *Cont.*

Genus/Species	Part of the Plant	Extraction Method	Major Compounds	Chemical Class	References
	Rhizomes	Hydrodistillation	Caryophyllene oxide (25.2%), humulene epoxide II (35.0%)	Sesquiterpene	[25]
Cyperus sesquiflorus (Torr.) Mattf. & Kük. (Syn. *Kyllinga odorata* Vahl)	Whole plant	Distillation	Dihydrokaranone (53.1%), aristolochene (11.3%)	Sesquiterpene	[81]
	Aerial parts	Hydrodistillation	Neopetasan (77.8%), aristolochene (10.9%)	Sesquiterpene	[82]
Cyperus tuberosus Rottb.	Rhizomes	Hydrodistillation	Humulene (30.04%), *β*-caryophyllene (12.13%)	Sesquiterpene	[83]
Eleocharis					
Eleocharis quinqueflora (Hartmann) O.Schwarz (Syn. *Eleocharis pauciflora* (Lightf.) Link)	Aerial parts	Hydrodistillation	Cyperene (35.4%), cyperotundone (12.7%), isorotundene (9.3%), cyperol (7.8%)	Sesquiterpene	[84]
Eleocharis uniglumis (Link) Schult.	Aerial parts	Hydrodistillation	Cyperene (28.8%), cyperotundone (8.9%), isorotundene (8.7%), cyperol (8.5%)	Sesquiterpene	[84]
Fimbristylis					
Fimbristylis falcata (Vahl) Kunth	Aerial parts	Steam distillation	Dehydroabietal (24.5%), dehydroabietol (4.9%)	Diterpene	[85]
Rhynchospora					
Rhynchospora colorata (L.) H.Pfeiff. (Syn. *Cyperus kyllingia* Endl.)	Roots, rhizomes	*n*-Hexane extraction	*α*-Cyperone (30.9%), *β*-selinene (28.1%), *α*-humulene (11.3%), *α*-copaene (8.5%)	Sesquiterpene	[29]
	Aerial parts	Hydrodistillation	*α*-Cadinol (19.32%), caryophyllene oxide (12.17%), *α*-muurolol (11.58%), *α*-humulene (9.85%)	Sesquiterpene	[86]
	Roots	Hydrodistillation	*α*-Cadinol (18.62%), caryophyllene oxide (12.18%), *α*-muurolol (11.56%), cyperene (10.15%)	Sesquiterpene	[21]
Schoenoplectus					
Schoenoplectus subulatus (Vahl) Lye (Syn. *Scirpus wardianus* J.R.Drumm.)	Aerial parts	Hydrodistillation	Cyperene (24.1%), cyperotundone (11.1%)	Sesquiterpene	[33]
Scleria					
Scleria hirtella Sw.	Not specified	Hydrodistillation	Nonanal (42.0%), geranial (25.3%), neral (15.3%)	Saturated fatty aldehyde, monoterpene	[87]
Scleria woodii C.B.Clarke (Syn. *Scleria striatonux* De Wild.)	Rhizomes	Hydrodistillation	Cyperene (8.0%), capric acid (6.0%)	Sesquiterpene, saturated fatty acid	[88]

[1] The scientific names of the species were verified on the website World Flora Online (WFO) Plant List (https://wfoplantlist.org/ (accessed on 1 November 2024)).

3.1. Chemical Composition of Essential Oils from Cyperaceae Species

In total, 72 major compounds were identified in the EOs of Cyperaceae species (Table 1). These phytochemicals belong to the following classes: sesquiterpenes (67%), monoterpenes (15%), diterpenes (10%), fatty acids (6%), phenolic compounds (1%), and benzenoids (1%) (Figure 2A). Among the plant parts used for the extraction of EOs, rhizomes were the most frequent (39%), followed by aerial parts (28%), tubers (14%), and roots (8%) (Figure 2B). Of all the species investigated, *C. rotundus* stood out for the largest number of studies on the chemical composition of its EOs (Figure 3). Regarding extraction methods, hydrodistillation using the Clevenger apparatus was the predominant technique. In some cases, methods such as steam distillation and extraction with *n*-hexane were also employed. The analysis of the chemical composition of EOs was performed mainly by gas chromatography coupled to mass spectrometry (GC-MS), consolidating itself as the standard technique to identify the chemical constituents of EOs from Cyperaceae species.

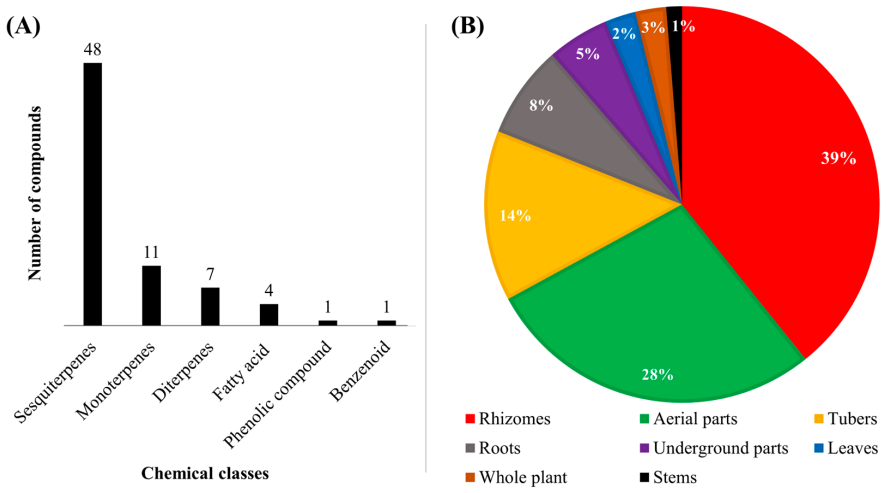

Figure 2. Representative classes of essential oils (**A**) and plant parts used (**B**) in the extraction of EOs from Cyperaceae.

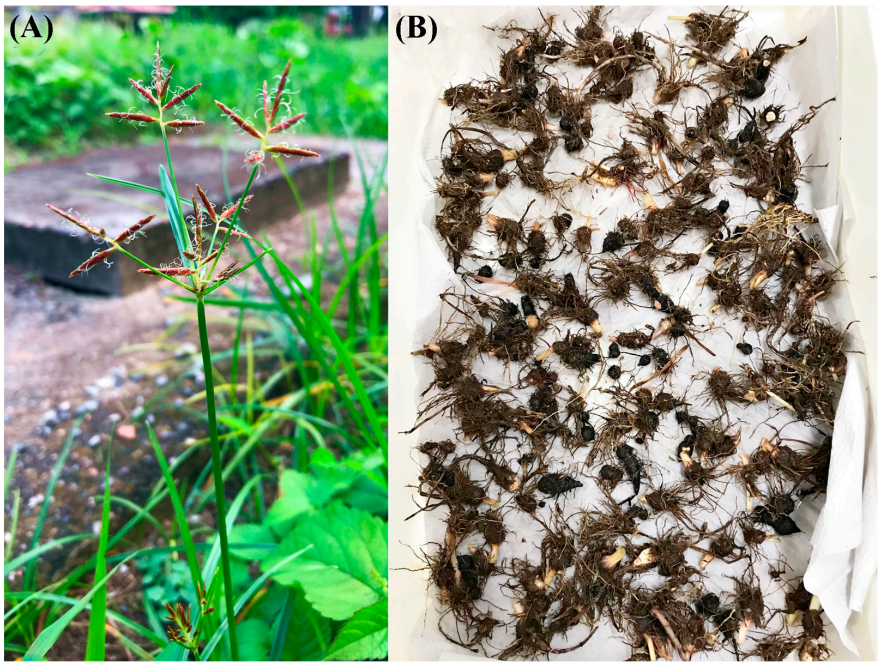

Figure 3. *Cyperus rotundus*. (**A**) Aerial part. (**B**) Tubers. Photos by: José Jailson Lima Bezerra.

3.1.1. Sesquiterpenes

As previously reported, sesquiterpenes represent the majority of compounds identified in EOs of Cyperaceae species, with an emphasis on cyperene, cyperotundone, caryophyllene oxide, mustakone, and α-humulene (Figure 4). Cyperene has been widely identified by GC-MS in EOs from several species, including *Carex pseudofoetida* Kük. [35], *Cyperus difformis* L. [36,50], *Cyperus arenarius* Retz. [36], *Cyperus articulatus* L. [39], *Cyperus esculentus* L. [40], *Cyperus capitatus* Vand. [50], *Cyperus compressus* L. [51], *Cyperus conglomeratus* Rottb. [52], *Cyperus distans* L.f. [54], *Cyperus giganteus* Vahl [60], *Cyperus papyrus* L. [67], *Cyperus rotundus* L. [71,77], and *Eleocharis uniglumis* (Link) Schult. [84]. Furthermore, cyperotundone has also been identified as one of the predominant compounds in several Cyperaceae species [23,24,37,60].

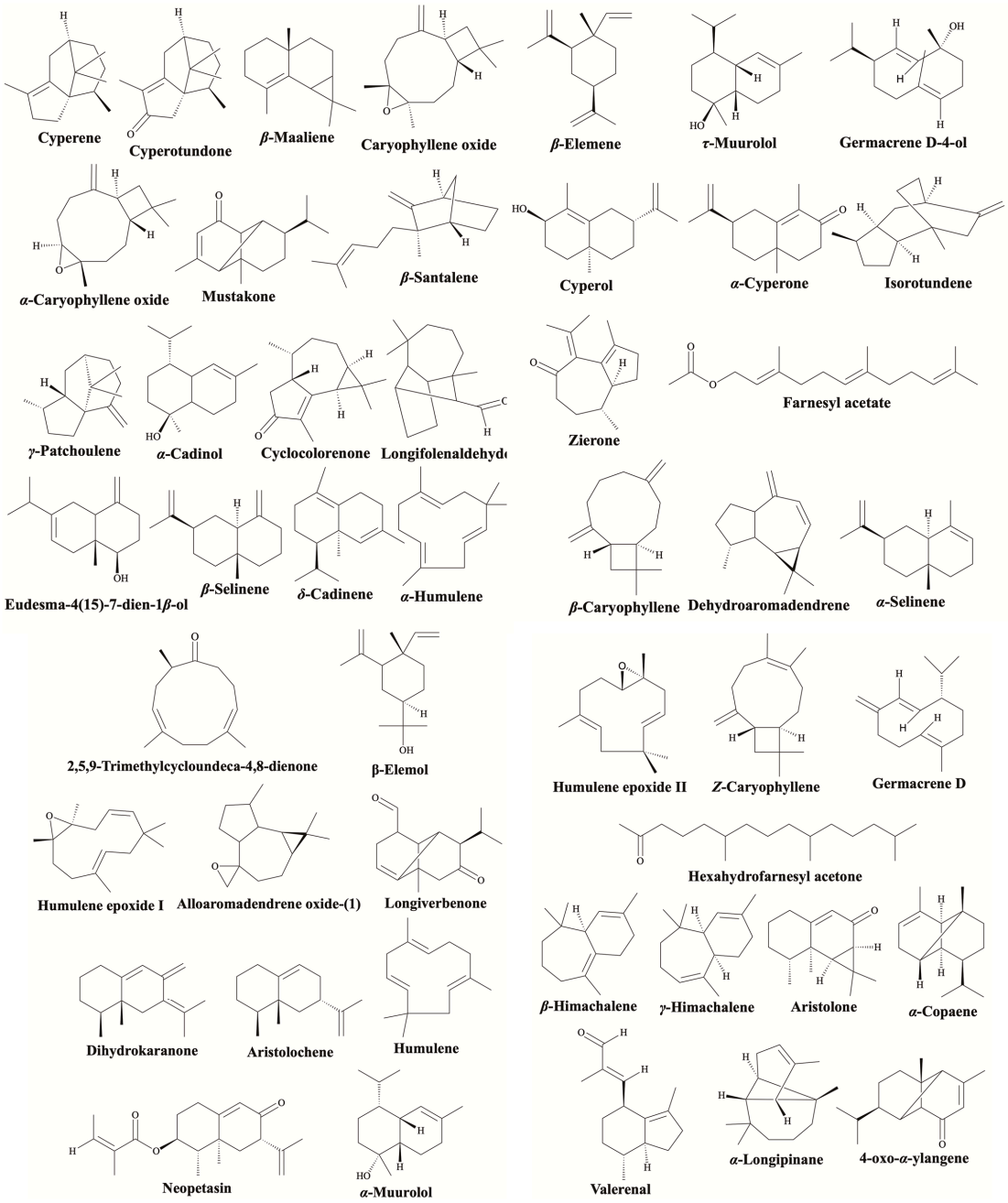

Figure 4. Sesquiterpenes identified in essential oils of Cyperaceae species.

The anticancer potential of sesquiterpenes isolated from *C. rotundus* has been documented. According to Ahn et al. [26], 6-acetoxy cyperene isolated from *C. rotundus* rhizomes induced apoptosis in human ovarian cancer cell lines, as demonstrated by the accumulation of A2780 and SKOV3 cells in the sub-G_1 phase. Additionally, treatment with this sesquiterpene stimulated the activation of caspase-3, caspase-8, caspase-9, and poly (ADP-ribose) polymerase, in a dose-dependent manner (40–120 μM). Shao et al. [28] observed that the combination of cyperotundone and adriamycin significantly inhibited the growth of MCF-7 cells, promoting cell cycle arrest and apoptosis, suggesting that cyperotundone may increase the sensitivity of chemotherapy in the treatment of breast cancer. Other studies have shown that combining natural products with synthetic anticancer drug formulations can enhance cancer cells' death rates [14,89]. This synergy improves cytotoxic effects, particularly in cells resistant to conventional treatments.

Another notable sesquiterpene is caryophyllene oxide, widely identified in the EOs of *Cyperus* species [25,38,40]. According to Pan et al. [90], this isolated compound showed high cytotoxicity against human osteosarcoma MG-63 cells, with IC_{50} values between 24.2 and 43.2 μM. Furthermore, the compound was effective in inhibiting cell migration and inducing apoptosis, evidenced by features such as cell shrinkage, formation of apoptotic bodies, and chromatin condensation. In an in vivo study, Xiu et al. [27] demonstrated that caryophyllene oxide significantly increased the tumor inhibition rate in treated mice (50–200 mg/kg) by suppressing the proliferation of HuH7 cells (hepatocellular carcinoma).

Mustakone was reported as the major component of EOs extracted from the rhizomes of *C. articulatus* [25,43–47]. Although studies indicate that the EO of *C. articulatus* has anticancer activity in vitro and in vivo against HepG2 cells [45], the cytotoxic effect of isolated mustakone has not yet been evaluated. On the other hand, Rukunga et al. [91] reported its promising antiplasmodial activity against *Plasmodium falciparum* (IC_{50} = 0.14 μg/mL), suggesting its use as a marker compound in antimalarial herbal medicines based on *C. articulatus*.

3.1.2. Monoterpenes

Similarly to sesquiterpenes, several monoterpenes were also identified in the EOs of Cyperaceae species (Figure 5). Analyses conducted by GC-MS indicated that α-pinene is one of the major compounds in the EOs of *C. articulatus* [38,42,45], *C. distans* [54], *C. esculentus* [58], and *C. rotundus* [73]. Regarding its anticancer activity, several studies have demonstrated that α-pinene has cytotoxic potential against different cell lines [92–96].

According to Chen et al. [92], α-pinene (8 mg/L) inhibited cell growth of the BEL-7402 cell line (hepatocellular carcinoma) by up to 79.3% in vitro. When tested in an in vivo xenograft model, it was observed that the monoterpene, at a dose of 2.67 mL/kg, inhibited tumor growth in mice by 69.1%. The authors also reported that a reduction in cyclin B protein in BEL-7402 cells is associated with cell cycle arrest in the G_2/M phases after α-pinene treatment. In a more recent study by Abe et al. [96], it was observed that α-pinene inhibited the proliferation of EL-4 and Molt-4 tumor cell lines (T cells). Furthermore, the compound induced mitochondrial dysfunction and the accumulation of reactive oxygen species and inhibited the translocation of the NF-κB p65 protein to the nucleus, leading to significant apoptosis in EL-4 cells. Zhao et al. [93] also observed that treatment with α-pinene, at a dose of 200 mg/kg, significantly inhibited the proliferation of the PC-3 cell line (prostate cancer) and induced apoptosis in an in vivo xenograft model.

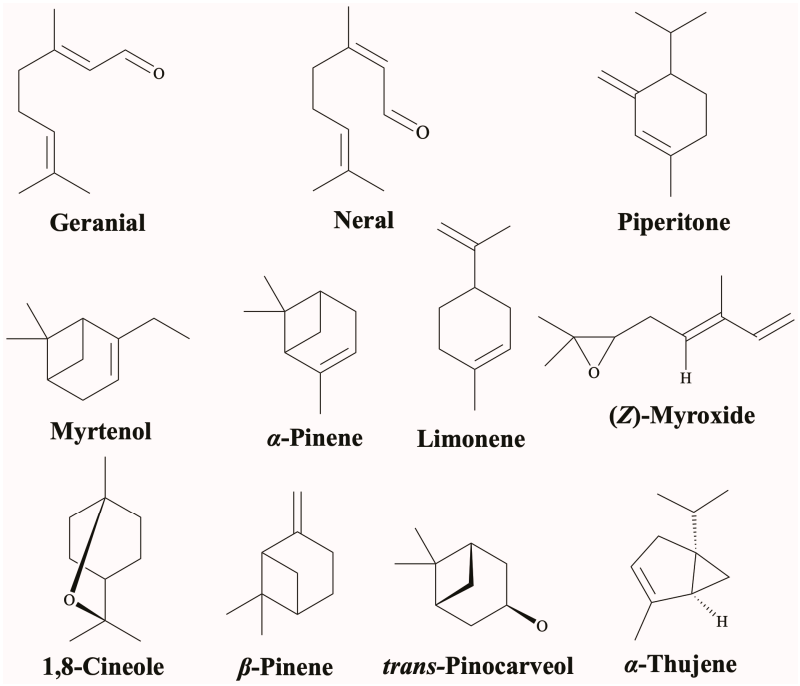

Figure 5. Monoterpenes identified in essential oils of Cyperaceae species.

3.1.3. Diterpenes

Seven compounds belonging to the diterpene class (Figure 6) were identified in the EOs of *Kyllinga brevifolia* Rottb. (*Cyperus brevifolius* (Rottb.) Hassk.) [41,48], *Kyllinga erecta* Schumach. (*Cyperus erectus* (Schumach.) Mattf. & Kük.) [56], *Cyperus laevigatus* L. [63], and *Fimbristylis falcata* (Vahl) Kunth [85]. Manoyl oxide was the main compound present in the EOs of *C. brevifolius* [41] and *K. erecta* [56]. According to Gani et al. [97], manoyl oxide showed anticancer potential in vitro and exhibited an IC_{50} of 50 µM against the MCF-7 cell line.

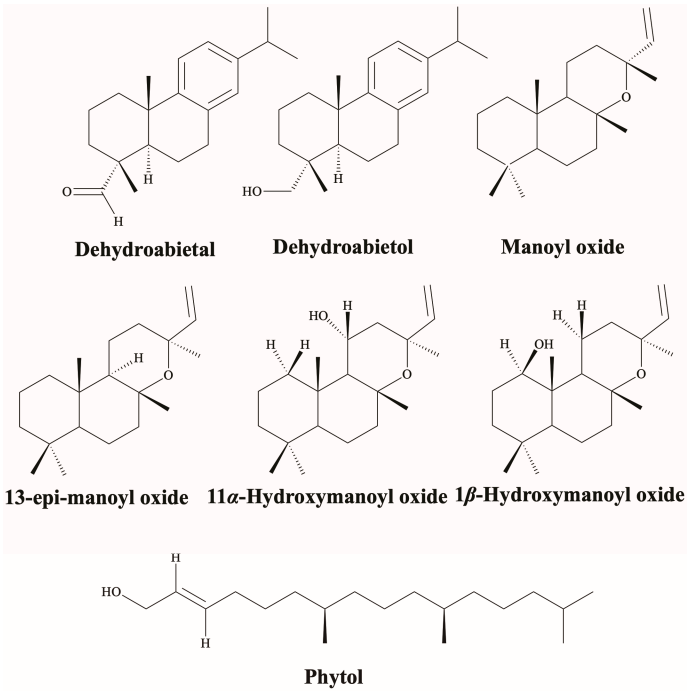

Figure 6. Diterpenes identified in essential oils of Cyperaceae species.

3.1.4. Fatty Acid

Compounds such as capric acid, nonanal, palmitic acid, and linolenic acid (Figure 7) were identified in the EOs of *Carex meyeriana* Kunth [34], *Scleria hirtella* Sw. [87], and *Scleria striatonux* De Wild. [88]. The anticancer activity of fatty acids has been widely reported in the literature [98–101]. Zhu et al. [100] reported that after 48 h of treatment, palmitic acid (0.1–50 μM) inhibited the growth of PC-3 and DU145 cell lines in a dose-dependent manner, exhibiting IC_{50} values of 10.72 and 16.83 μM, respectively. According to Wang et al. [101], the main anticancer mechanism of palmitic acid involves the induction of cellular apoptosis via the mitochondrial pathway and interference with the cancer cell cycle, predominantly resulting in cell cycle arrest in the G_1 phase.

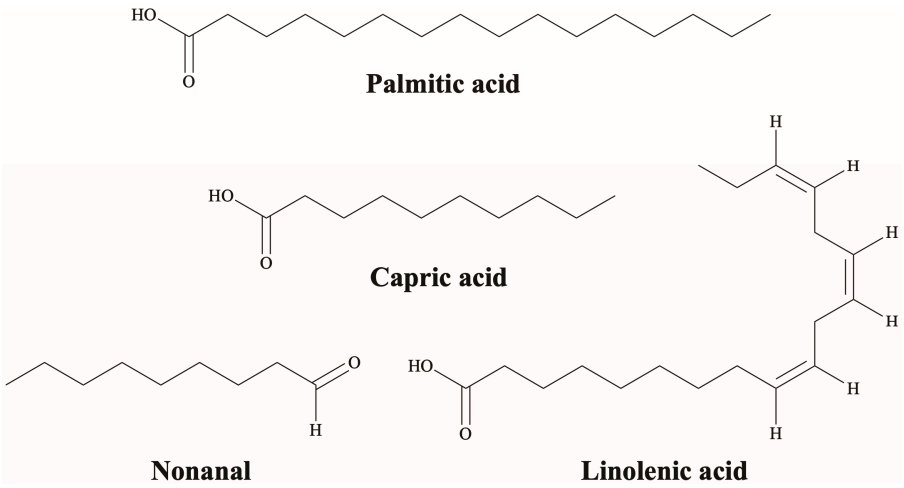

Figure 7. Fatty acids identified in essential oils of Cyperaceae species.

3.1.5. Phenolic Compound and Benzenoid

The phenolic compound eugenol was identified in the EO of the rhizomes of *Cyperus conglomeratus* Rottb. [53], while the benzenoid remirol stood out as the major compound of the EO of *Remirea maritima* Aubl. (*Cyperus pedunculatus* (R.Br.) J.Kern) [68] (Figure 8). Several studies have already reported the anticancer properties of eugenol [102–104]. This potential is mainly attributed to its antimetastatic, antiproliferative, antiangiogenic, anti-inflammatory, cell cycle arrest induction, apoptotic, and autophagic effects [103]. According to Padhy et al. [104], eugenol acts on multiple signaling pathways to exert its anticancer effects, the major ones being the MAPK/ERK, JNK/STAT3, WnT/β-Catenin pathway, E2F1/survivin, and NF-κB signaling cascades.

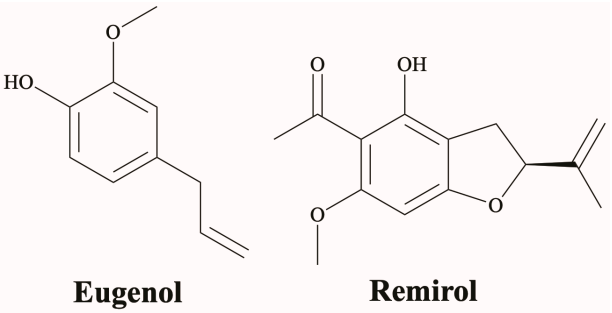

Figure 8. Phenolic compound and benzenoid identified in essential oils of Cyperaceae species.

3.2. Anticancer Activity of Essential Oils from Cyperaceae Species

The anticancer activity, both in vitro and in vivo, of EOs from four Cyperaceae species is well documented in the literature (Table 2). Significant results were observed on murine

melanoma (B16-F10), colon cancer (HCT-116 and HT-29), cervical cancer (HeLa), hepatocellular carcinoma (HepG2), human promyelocytic leukemia (HL-60), leukemia (L1210), breast carcinoma (MCF-7 and MDA-MB231), lung carcinoma (NCI-H187), prostate carcinoma (PC-3), and neuroblastoma (SH-SY5Y) cell lines. Based on the evaluation criteria of Boik [31] and Niksic et al. [32], the EO of *C. rotundus* demonstrated high cytotoxic activity against HCT-116 (IC_{50} = 1.06 µg/mL), HepG2 (IC_{50} = 1.17 µg/mL), MCF-7 (IC_{50} = 2.22 µg/mL), and HeLa (IC_{50} = 8.307 µg/mL) cell lines [20,105]. Furthermore, the EO of *C. kyllingia* exhibited significant potential against NCI-H187 (IC_{50} = 6.7 µg/mL) and MCF-7 (IC_{50} = 13.3 µg/mL) cells [21]. In contrast, EOs from other species showed IC_{50} values exceeding 20 µg/mL against cancer cells, suggesting they are not suitable for further antitumor activity testing in in vivo experimental models.

Table 2. Anticancer activity of Cyperaceae species essential oil.

Species	Part of the Plant	Major Compounds in EOs	Concentrations or Doses	Method	Cancer Cell Lines	Results	References
Cyperus articulatus L.	Rhizomes	Mustakone (11.60%)	0.4–50 µg/mL	Alamar blue (in vitro)	HepG2, HCT-116, MCF-7, HL-60, B16-F10	HepG2 (IC_{50} = 28.5 µg/mL), HCT-116 (IC_{50} = >50 µg/mL), MCF-7 (IC_{50} = 36.7 µg/mL), HL-60 (IC_{50} = 33.51 µg/mL), B16-F10 (IC_{50} = 39.7 µg/mL)	[45]
	Rhizomes	Mustakone (11.60%)	40 and 80 mg/kg	Xenograft model (in vivo)	HepG2	Tumor inhibition: 46.5–50.0%	[45]
Cyperus longus L.	Whole plant	Not reported	12.5–200 µg/mL	MTT (in vitro)	PC-3, MCF-7	PC-3 (IC_{50} = 39.91–43.65 µg/mL), MCF-7 (IC_{50} = 12.55–31.35 µg/mL)	[65]
Cyperus rotundus L.	Tuber	α-Cyperone (25.23%), cyperene (20.38%)	50–800 µg/mL	MTT (in vitro)	L1210	IC_{50} = 49 µg/mL	[72]
	Tuber	α-Cyperone (21.1%)	1.56–100 µg/mL	CVS (in vitro)	HCT-116, HepG2, MCF-7	HCT-116 (IC_{50} = 1.06 µg/mL), HepG2 (IC_{50} = 1.17 µg/mL), MCF-7 (IC_{50} = 2.22 µg/mL)	[20]
	Rhizomes	2,5,9-Trimethylcycloundeca-4,8-dienone (13.44%)	50 or 200 mg/mL	MTT (in vitro)	MCF-7, MDA-MB231, HT-29, HCT-116	MCF-7 (IC_{50} = 41.28 µg/mL), MDA-MB231 (IC_{50} = 44.31 µg/mL), HT-29 (IC_{50} = 28.81 µg/mL), HCT-116 (IC_{50} = 21.33 µg/mL)	[75]
	Rhizomes	α-Cyperone (38.46%)	50–1000 µg/mL	MTT (in vitro)	SH-SY5Y	Decreased cell viability at concentrations above 150 µg/mL	[77]
	Tubers	Not reported	3.9–500 µg/mL	MTT (in vitro)	HeLa	IC_{50} = 35.062 µg/mL	[106]
	Rhizomes	Humulene epoxide (38.43%), caryophyllene oxide (21.03%)	Not specified	MTT (in vitro)	HepG2, MCF-7, PC-3	HepG2 (IC_{50} = 204.1 µg/mL), MCF-7 (IC_{50} = 170.8 µg/mL), PC-3 (IC_{50} = >1000 µg/mL)	[79]
	Rhizomes	Not reported	0.625–80 µg/mL	MTT (in vitro)	HeLa	IC_{50} = 8.307 µg/mL	[105]
Rhynchospora colorata (L.) H.Pfeiff. (Syn. *Cyperus kyllingia* Endl.)	Roots	α-Cadinol (18.62%), caryophyllene oxide (12.18%)	5 µL	REMA (in vitro)	NCI-H187, MCF-7	NCI-H187 (IC_{50} = 6.7 µg/mL), MCF-7 (IC_{50} = 13.3 µg/mL)	[21]

CVS: crystal violet staining. EOs: essential oils. IC_{50}: inhibitory concentration 50%. MTT: 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide. REMA: resazurin microplate assay. Cancer cell lines: B16-F10: mouse melanoma. HCT-116: colon cancer. HeLa: cervical cancer. HepG2: hepatocellular carcinoma. HL-60: human promyelocytic leukemia. HT-29: colon cancer. L1210: leukemia. MCF-7: breast carcinoma. MDA-MB231: breast cancer. NCI-H187: lung carcinoma. PC-3: prostate carcinoma. SH-SY5Y: neuroblastoma.

The mechanisms of action of EOs from Cyperaceae species possibly involve DNA fragmentation, cell cycle arrest, and induction of apoptosis (Figure 9). Kilani et al. [72]

reported that a 50 µg/mL concentration of EO from *C. rotundus* tubers caused DNA fragmentation and apoptosis in L1210 cells (leukemia). Memariani et al. [65] observed that EO from the whole plant of *C. longus* significantly inhibited the proliferation of MCF-7 cells, with an IC_{50} of 12.55 µg/mL after 48 h of exposure. Furthermore, at a concentration of 75 µg/mL, EO from *C. longus* induced apoptosis in MCF-7 (78.23%) and PC-3 (65.35%) cells. Nogueira et al. [45] reported that concentrations of 12.5, 25, and 50 µg/mL of EO from *C. articulatus* rhizomes induced DNA fragmentation in HepG2 cells by up to 22.0, 26.0, and 36.4%, respectively. This same cell line showed cell cycle arrest in the G_2/M phase after treatment with EO.

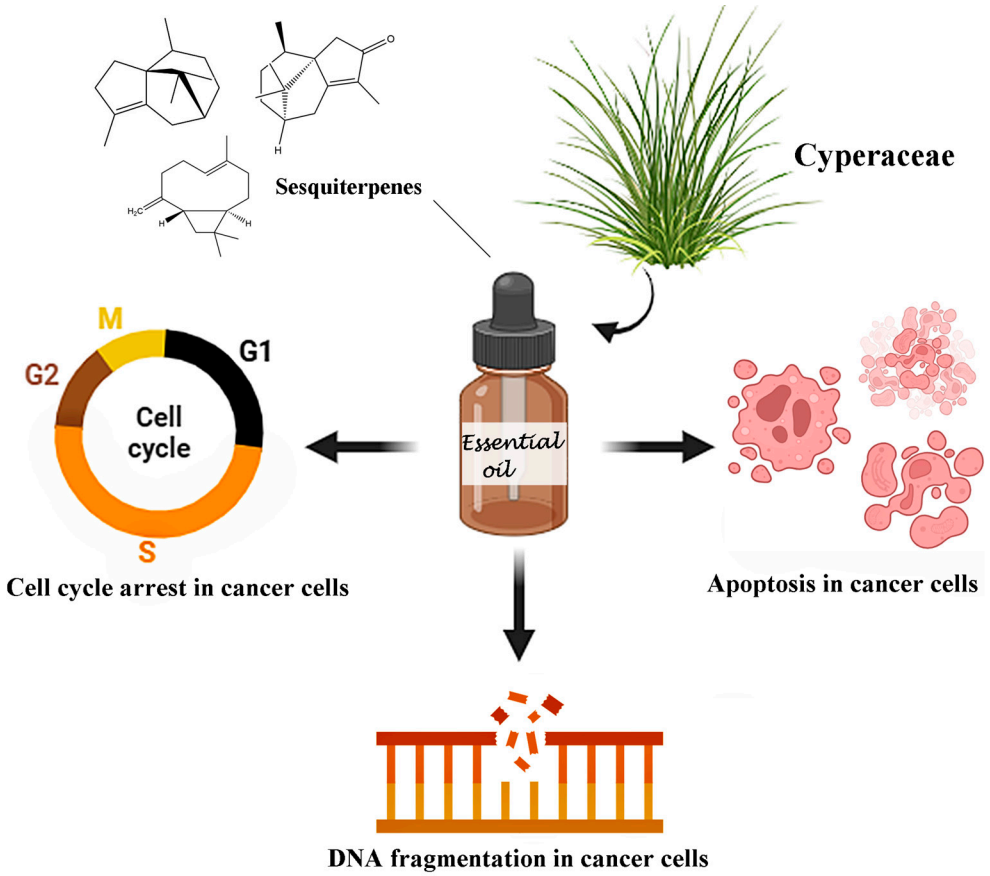

Figure 9. Mechanisms of action of essential oils from Cyperaceae species against cancer cell lines. Illustration created by Dr. José Jailson Lima Bezerra in BioRender.com.

In the literature, there is only one study reporting the in vivo anticancer activity of the EOs of Cyperaceae. Nogueira et al. [45] evaluated the antitumor potential of EO from *C. articulatus* rhizomes in an experimental xenograft model with HepG2 cells (hepatocellular carcinoma). According to these authors, C.B-17 mice treated with EO at doses of 40 and 80 mg/kg intraperitoneally, showed tumor inhibition rates of 46.5 and 50.0%, respectively. These values were similar to those in the positive control group treated with the standard drug 5-fluorouracil (5-FU, 10 mg/kg), for which there was a tumor mass inhibition rate of 44.2%. These findings indicate the potential of EO of *C. articulatus* as a promising natural alternative for the treatment of liver cancer [45].

Nanotechnological applications in formulations containing EOs from Cyperaceae species may be an effective alternative to increase the potential of these natural products against cancer cells. According to Sharma et al. [14], EOs have an unsurpassed potential for cancer treatment when administered in the form of nanoencapsulation (nanoemulsions, niosomes, nanoparticles, and liposomes), as these products act on target cancer cells and

mediate the release of specific drugs. Some studies have reported that nanoparticles derived from natural compounds offer several advantages, including greater stability, solubility in biological media, controlled release of encapsulated compounds, greater cellular uptake, and the ability to overcome biological barriers [12,107,108]. However, it is important to emphasize that the exact mechanism for the synthesis of metal nanoparticles by terpenoids in EO is not yet fully elucidated. But it is likely that terpenoids may play a key role in the reduction of bivalent metals to zero-valent metal atoms in phytochemical reduction reactions [109].

3.3. Acute Oral Toxicity of Essential Oils from Cyperaceae Species

Although several studies have investigated the chemical composition of EOs from Cyperaceae species, there is a gap regarding the assessment of the acute toxicity in vivo of these products. In the literature, only the EO of *C. articulatus* has been studied in this context, showing no serious toxic effects at doses of up to 2000 mg/kg administered orally in rodents [43,47,110]. According to Metuge et al. [110], among six mice treated with EO from *C. articulatus* rhizomes, only one presented rough hair and weight loss in the first days after administration. However, it was observed that the mice remained active, healthy, and showed continuous weight gain. No significant behavioral changes were recorded, and no deaths occurred during the 14 days of follow-up.

Silva et al. [43] demonstrated that Balb/c mice orally treated with doses of 50, 300, and 2000 mg/kg of EO from *C. articulatus* rhizomes did not exhibit clinical changes, weight loss, or mortality throughout the experimental period. Similarly, Ferreira et al. [47] observed that Swiss mice and Wistar rats treated with 2000 mg/kg of EO also showed no signs of toxicity, changes in body weight, or deaths during the 14 days of follow-up. These results indicate that the EO of *C. articulatus* is biologically safe. More research is needed to explore its potential as an herbal medicine in the treatment of inflammation, nociception, and cancer.

Despite the scarcity of investigations related to volatile oils from other Cyperaceae species, the acute toxicity of different polar and nonpolar extracts of *C. rotundus* and *C. esculentus* have already been well reported in the literature [111–114]. These products have also demonstrated a broad spectrum of in vitro and in vivo biological activities and biological safety in rodents.

4. Conclusions and Future Perspectives

The essential oils from 33 Cyperaceae species showed a wide diversity of major compounds in their chemical composition. These phytochemicals belong to the classes of sesquiterpenes, monoterpenes, diterpenes, fatty acids, phenolic compounds, and benzenoids. Among the sesquiterpenes, the major compounds were cyperene, cyperotundone, caryophyllene oxide, and mustakone, identified in several species.

From a pharmacological point of view, EOs from *Cyperus rotundus*, *C. kyllingia*, and *C. longus* exhibited high cytotoxic activity in vitro against the HCT-116, HepG2, MCF-7, HeLa, and NCI-H187 cell lines. In this perspective, the EOs from these species are strongly recommended for in vivo evaluation of their anticancer potential. Molecular findings suggest that the mechanisms of action associated with EOs of Cyperaceae include DNA fragmentation, cell cycle arrest, and induction of apoptosis.

To date, only the EO from *C. articulatus* has been investigated for its in vivo antitumor potential and acute toxicity in rodents. Consequently, further preclinical research is urgently needed to evaluate the anticancer activity of EOs from other Cyperaceae species with high in vitro cytotoxicity. Additionally, studies on acute oral toxicity are essential to assess biological safety and determine potential side effects.

Considering that the Cyperaceae family comprises approximately 5687 species, it is evident that it is underexplored both in chemical and pharmacological terms, revealing vast potential for future research.

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