Euphorbia

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Contributor: Adedayo Ademiluyi

Euphorbia genus (Euphorbiaceae family), which is the third largest genus of angiosperm plants comprising ca. 2000 recognized species, is used all over the world in traditional medicine, especially in the traditional Chinese medicine. Members of this taxa are promptly recognizable by their specialized inflorescences and latex. In this review, an overview of Euphorbia-derived natural products such as essential oils, extracts, and pure compounds, active in a broad range of biological activities, and with potential usages in health maintenance, is described. The chemical composition of essential oils from Euphorbia species revealed the presence of more than 80 phytochemicals, mainly oxygenated sesquiterpenes and sesquiterpenes hydrocarbons, while Euphorbia extracts contain secondary metabolites such as sesquiterpenes, diterpenes, sterols, flavonoids, and other polyphenols.

Keywords: Euphorbia ; essential oils ; extracts ; phytochemicals ; terpenoids ; bioactivity ; antimicrobial ; anti-inflammation ; anticancer ; antioxidant ; phytoconstituents

1. Introduction

The genus *Euphorbia* (Euphorbiaceae) is the third major genus of flowering plants, with 1836 accepted species [1][2], subdivided into many subgenera and sections. This genus has a worldwide distribution and can be found in all temperate and tropical regions. Also, this group of plants is characterized by an extraordinary variety of forms, from small ephemerals to several forms of herbaceous annuals or perennials, big shrubs, small trees, cushion-forming subshrubs, and cactus-like succulents [3]. From the 243 *Euphorbia* species assessed by the IUCN Red List of Threatened species, 170 (70%) are threatened with extinction (categories vulnerable, endangered, and critically endangered) [4].

More than 5% of species of *Euphorbia* are used in traditional medicine, mainly as emetic and purgative agents, to treat digestive and respiratory disorders, skin and inflammatory conditions, migraine, intestinal parasites and gonorrhoea, and as wart cures [5][6][7][8][9]. The usable parts of the *Euphorbia* species include roots, seeds, latex, wood, barks, leaves, and whole plants [5][6][7][8][9]. A brief overview of traditional medicine applications of *Euphorbia* is described in Section 2.

Euphorbia species have these curative properties due to the presence of various phytochemicals, which constitute the secondary metabolites of these plants [1][10][11][12][13][14][15][16][17]. They belong mainly to the terpenoids, flavonoids and polyphenols classes which also exhibit a great variety of biological effects such as cytotoxic, mammalian mitochondrial respiratory chain inhibition, HIV-1 and bacterial infection inhibition, anti-inflammatory, multidrug resistance modulators [13][18][19][20][21][22][23]. In fact, there is a good attention in *Euphorbia*-derived metabolites mainly because of the diterpene ingenol mebutate identified on *E. peplus* L. (as well as on *E. lathyris* L., *E. nivulia* Buch.-Ham., *E. esula* L., *E. antiquorum* L., *E. serpens* Kunth, and *E. fischeriana* Steud.), and is the active ingredient of Picato® medicine used in topical therapy against the precancerous skin condition actinic keratosis [24][25][26]. However, some *Euphorbia* compounds are toxic, resulting from an evolutionary strategy of plant defence against predators (e.g., herbivores), compounds that have a caustic and irritating effect to the skin and promote tumours [10][27].

Euphorbia plants are easily distinguishable by their toxic and highly skin irritant milky latex and particular inflorescences, designated as cyathia [28][29], and are widely used as ornamental plants, such as *E. milii* Des Moul., *E. tirucalli* L., and *E. lactea* Roxb [30]. The latex is the most valuable product obtained from *Euphorbia* species despite being toxic, it contains several biologically active natural compounds, such as triterpenoids [31]. Besides, latex is used in commercially valuable products like paints and natural rubber (intisy rubber obtained from *E. intisy* Drake) [30][32].

Secondary metabolites contained in *Euphorbia* plants also potentiate their use for food preservation. According to Toro-Vazquez et al. [33], candelilla wax obtained from the leaves of some species of *Euphorbia* found in Northern Mexico and the Southwest of the United States was recognized by the Food and Drug Administration (FDA) as a food additive with gelling properties, forming oleo-gels together with vegetable oils. According to EU regulations, candelilla wax is assigned

by E902 additive code, and it is also an allowed glazing agent, applied on the surface of confectionery, nuts, wafers, coffee grains, dietary supplements, and fresh fruit [34].

2. Traditional Medicine Uses of *Euphorbia* Plants

The *Euphorbia* genus is well-known to involve several plants used in folk medicine in different parts of the world, especially in traditional Chinese medicine [5][7][9]. Moreover, a recent study discriminated the global geographical distribution regarding uses of *Euphorbia* plants in traditional medicine [6]. In this regard, three particular uses were most often detected, such as (1) treatments of digestive system disorders (very globally frequent excepting Australasia); (2) as remedies for infections/infestations (mainly in Southern Africa and America, Pacific, Asia-tropical, and Asia-temperate); and (3) for treating skin/subcutaneous cellular tissue disorders (particularly in Australasia, Europe, Asia, and Northern America). On the other hand, within the 33 species with citations in folk practices worldwide, the three most-referenced plants used as traditional medicines were *E. hirta* L., *E. thymifolia* L., and *E. lathyris* [6].

Euphorbia hirta whole plant has been employed in Burundi, China, Philippines, and Nigeria to manage diarrhoea [35][36][37][38], while *E. hirta* decoction is used in Vietnam, India, and Mozambique to treat dysentery [39][40][41] and to treat bronchitis/asthma/coughs in Nepal, Australia, the South Western United States, and Hawaii [6][39][42]. Additionally, the latex from *E. hirta* is also applied to treat skin diseases and fever mostly in Asia [6] and to treat gonorrhoea in Malaysia [43] and other conditions such as malaria, candidiasis, and ringworm infections [6]. Populations aroundthe Vellore District of Tamil Nadu, India, use decoction of the *E. hirta* whole plant to treat poisonous snakebites (topically and orally administration) [44].

Despite the registered abortifacient properties of *E. thymifolia* decoctions in Chile, its latex or leaf decoctions have been recorded as lactation stimulants in different continents [45]. In the case of *E. lathyris*, emetic and purgative actions have been described in Europe as well as its seeds used to treat snakebites, ascites, schistosomiasis, and hydropsy [38][46].

Euphorbia maculata L. in Northern America is used for the treatment of corneal opacities and warts [47], while in China, it is used to treat blood disorders (e.g., haematuria, haemoptysis, epistaxis, and hemafecia), carbuncles, and wounds [38]. *Euphorbia denticulata* Lam. and *E. macrocarpa* Boiss. & Buhse are also used for wound healing in Turkey [48], and a similar use is reported in Ethiopia for *E. heterophylla* L. and *E. prostrata* Aiton [49].

The decoction, unguent, or hot steam of other *Euphorbia* species are used on inflammation conditions, such as *E. corollata* L. (for dropsy), *E. marginata* Pursh, and *E. antiquorum* (for swellings) [6]. Similarly, *E. antiquorum* is utilized in Vietnam to alleviate toothache events [41] as well as for treating cutaneous dropsy, cutaneous infections, cancer, and liver ailment [50]. *E. tirucalli* L. and *E. ingens* E.Mey. ex Boiss. like *E. lathyris*, can be used as an emetic against snakebites [39][51]. A recent review has been published showing that *E. tirucalli* (whole plant and its parts individually separated) has some records in South America, India, the Middle East, and Africa regarding beneficial effects on leprosy, syphilis, cancer, asthma, and intestinal parasites [51]. The same research group [52] also published a review where they report the various applications in traditional medicine of *E. neriifolia* L. Its latex is used as a carminative and expectorant, as well as in the treatment of tumours, abdominal and skin problems, leprosy, asthma, and kidney stones, while the roots are used in the treatment of scorpion stings and snake bites. The leaves can also be used as carminative and in the treatment of pain, inflammation, bronchial infections and lack of appetite [52]. *Euphorbia helioscopia* L. is used in the traditional Chinese medicine in situations of bacillary dysentery, osteomyelitis, and malaria [53]. In Uyghur medicine, China, *E. resinifera* O.Berg is recurrently employed to suppress tuberculosis, toothache, and chronic pain [54], while *E. fischeriana* have been used as a remedy for cancer, ascites, and oedema [55], and *E. granulata* Forssk. is utilized against intestine worms, oedema, cough, blood impurities, and renal diseases [56][57].

However, some *Euphorbia* plants, especially their latex or milky sap (e.g., *E. hirta*, *E. helioscopia, E. royleana* Boiss. among others), are considered as irritating materials for skin, mouth, and throat, causing burning sensation, acute inflammation (even blisters), and nausea [58]. In veterinary medicine, *E. milii* Des Moul. and *E. nivulia* is used to treat diarrhoea and wounds in livestock, respectively, but other *Euphorbia* species can produce irritations [6].

3. *Euphorbia* Plants: Essential Oil Composition and Activities

Researchers from various countries worldwide have studied the chemical composition of essential oils (EOs) from different *Euphorbia* species. An overview of their most abundant components (the content higher than 5%) along with the most relevant biological activities to health maintenance (when available, and when the biological activity of a positive

standard compound was also presented) is given in **Table 1**. The chemical structure of the major constituents of EOs from *Euphorbia* species whose content is higher than 25% is depicted in **Figure 1**.

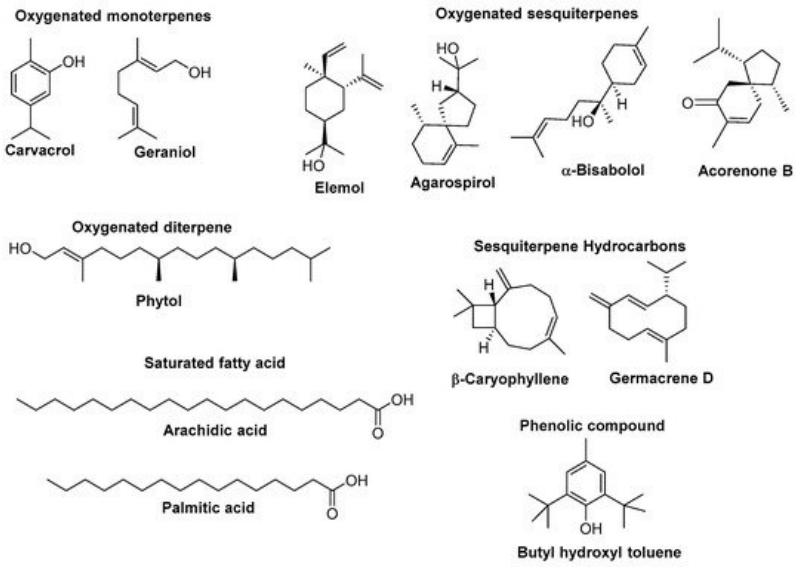

Figure 1. Chemical structures of the constituents of *Euphorbia* essential oil, each one with a content exceeding 25%.

Table 1. Chemical composition and biological activities of *Euphorbia* essential oils.

Species	Origin	Raw Material	Extraction Method	Main Components [a] (%)	Most Relevant Biological Activities	Ref.
***E. acanthothamnos* Heldr. & Sart. ex Boiss.**	**Greece**	**Inflorescences**	**Steam distillation**	**Phytol (28.3), phytol acetate (9.3), β-caryophyllene (7.5)**	**not evaluated**	[59]
***E. apios* L.**	**Greece**	**Inflorescences**	**Steam distillation**	**Germacrene D (30.0), heptacosane (12.7), β-caryophyllene (10.0), tricosane (6.5), pentacosane (6.0)**	**not evaluated**	[59]
***E. characias* L.**	**Greece**	**Inflorescences**	**Steam distillation**	**Nonanal (22.8), phytol (13.5), pentacosane (8.5), heptacosane (7.4), palmitic acid (5.7), nonacosane (5.6)**	**not evaluated**	[59]
***E. cotinifolia* L. (syn. *E. caracasana* (Klotzsch & Garcke) Boiss.)**	**Venezuela**	**Leaves**	**Hydro-distillation**	**β-Caryophyllene (39.3), germacrene-D (21.5%), α-copaene (9.3), α-humulene (5.2)**	**not evaluated**	[60]
***E. dendroides* L.**	**Greece**	**Inflorescences**	**Steam distillation**	**Heptacosane (10.5), pentacosane (6.0), 4-terpineol (5.5), tricosane (5.0)**	**not evaluated**	[59]
***E. densa* Schrenk**	**Syria**	**Aerial parts**	**Hydro-distillation**	**1,8-Cineole (18.87), linalool (13.61), carvacrol (13.32), (*E*)-caryophyllene (10.29)**	**Radical scavenging activity (EC_{50} = 0.35 μg/mL) lower than BHA (EC_{50} = 0.135 μg/mL)**	[61]
***E. fischeriana* Steud.**	**China**	**Roots**	**Steam distillation**	**Eudesmol (18.22), *p*-menth-8-en-2-ol (9.36), caryophyllene oxide (8.61), selinenol (6.83)**	**Radical scavenging activity (IC_{50} = 57.2 μg/mL) similar to ascorbic acid (IC_{50} = 63.1 μg/mL) but lower than BHT (IC_{50} = 26.1 μg/mL)**	[62]
***E. fragifera* Jan**	**Italy**	**Inflorescences**	**Steam distillation**	**Carvacrol (61.55), carvon (9.22), β-caryophyllene (5.80)/geraniol (59.65), β-caryophyllene (9.05)**	**not evaluated**	[63]

Species	Origin	Raw Material	Extraction Method	Main Components [a] (%)	Most Relevant Biological Activities	Ref.
E. gaillardotii Boiss. & Blanche	Turkey	Aerial parts	Hydro-distillation	Arachidic acid (32), hexatriacontane (8.7), mint furanone (8.4), palmitic acid (8.0), tetratetracontane (6.2), octadecane (5.6), α-silenene (5.2)	Anti-lipid peroxidation activity (IC_{50} = 14.8 µg/mL) similar to α-tocopherol, but much lower radical scavenging activity than BHT.	[64]
E. golondrina L.C.Wheeler	Cameroon	Leaves	Steam distillation	Caryophyllene oxide (14.16), 2-pentadecanone (13.78), camphor (9.41), phytol (5.75)	not evaluated	[65]
E. hebecarpa Boiss.	Iran	Aerial parts	Hydro-distillation	α-Bisabolol (31.2), *cis*-cadin-4-en-7-ol (20.1), *trans*-piperitol (8.6), cis-*p*-menth-2-en-1-ol (6.4), *trans*-*p*-menth-2-en-1-ol (6.2)	not evaluated	[66]
E. helioscopia L.	Greece	Inflorescences	Steam distillation	Phytol (21.2), β-caryophyllene (10.0), behenic acid methyl ester (8.1), myristic acid methyl ester (5.5)	not evaluated	[59]
E. helioscopia L.	Turkey	Aerial parts	Hydro-distillation	β-Cubebene (19.3), palmitic acid (12.2), caryophyllene oxide (11.7), τ-elemene (9.3), spathulenol (9.3), phytol (6.9), hexahydrofarnesly acetone (5.3)	Low antioxidant and antiacetylcholinesterase activity, moderate butyrylcholinesterase and similar anti-urease activity to thiourea.	[67]
E. heterophylla L.	Nigeria	Leaves	Hydro-distillation	3,7,12,15-Tetramethyl-2-hexadecen-1-ol (12.30), stearic acid (11.21), oleic acid (10.42), linoleic acid (8.97), 1,2-epoxy-cyclododecane (7.91), 13-tetradece-11-yn-1-ol (7.83), 7,10-hexadecadienal (7.62), 1,2,15,16-diepoxyhexadecane (6.37), phytol (6.32), 2-monopalmitin (5.43)	Toxic to brine shrimp larvae (LC_{50} = 21.7 µg/mL). Radical scavenging activity similar to ascorbic acid, lower than BHA but higher than α-tocopherol at 250 µg/mL.	[68]
E. heterophylla L.	Nigeria	Stems	Hydro-distillation	Stearic acid (11.21), oleic acid (10.42), linoleic acid (8.97), 1,2-epoxy-cyclododecane (7.91), 13-tetradece-11-yn-1-ol (7.83), 7,10-hexadecadienal (7.62), 1,2,15,16-diepoxyhexadecane (6.37), phytol (6.32), 2-monopalmitin (5.43), 2-aminoethoxyethynediyl methyl ester (5.40)	Very toxic to brine shrimp larvae (LC_{50} = 8.94 µg/mL). Radical scavenging activity similar to ascorbic acid, lower than BHA but higher than α-tocopherol at 250 µg/mL.	[68]
E. heterophylla L.	Egypt	Aerial parts	Hydro-distillation	1,8-Cineole (32.0), camphor (16.5), β-elemene (5.9)	Radical scavenging activity (IC_{50} 325.3 µL/L) lower than ascorbic acid (204.4 µL/L).	[69]
E. hirta L.	Lagos	Leaves	Hydro-distillation	Phytol and its isomeric forms (34.8), 6,10,14-trimethyl-2-pentadecanone (12.37), hexadecanal (7.63), palmitic acid (6.26)	not evaluated	[70]

Species	Origin	Raw Material	Extraction Method	Main Components [a] (%)	Most Relevant Biological Activities	Ref.
***E. macroclada* Boiss.**	**Turkey**	**Aerial parts**	**Hydro-distillation**	**Tetratetracontane (42.7), hexatriacontane (12), mint furanone (6.0)**	**Anti-lipid peroxidation activity (IC_{50} = 14.8 µg/mL) similar to α-tocopherol. Lower radical scavenging activity than BHT but higher than *E. gaillardotii* essential oil.**	[64]
***E. macrorrhiza* C.A.Mey. ex Ledeb.**	**China**	**Aerial parts**	**Hydro-distillation**	**Acorenone B (16.72), (+)-cycloisosativene (14.94), 3β-hydroxy-5α-androstane (10.62), β-cedrene (8.40), copaene (7.37), palmitic acid (5.68)**	**Cytotoxic activity against Caco-2 cell line (IC_{50} = 78.32 µg/mL), antibacterial activity against *Staphyloccocus aureus* (MIC = 5.6 µg/mL) but lower than ampicillin (MIC = 0.25 µg/mL)**	[71]
***E. macrorrhiza* C.A.Mey. ex Ledeb.**	**China**	**Roots**	**Hydro-distillation**	**Acorenone B (25.80), (+)-cycloisosativene (12.40), β-cedrene (7.98), copaene (6.29), 3β-hydroxy-5α-androstane (5.52)**	**Cytotoxic activity against Caco-2 cell line (IC_{50} = 11.86 µg/mL), antibacterial activity against *Staphyloccocus aureus* (MIC = 2.8 µg/mL) but lower than ampicillin (MIC = 0.25 µg/mL)**	[71]
***E. pekinensis* Rupr.**	**China**	**Roots**	**Steam distillation**	**Agarospirol (49.23), hedycargol (20.66)**	**not evaluated**	[72]
***E. pilosa* L.**	**India**	**Aerial parts**	**Hydro-distillation**	**Phytol (5.75), *n*-pentadecanal (5.12)**	**not evaluated**	[73]
***E. rigida* M.Bieb.**	**Greece**	**Inflorescences**	**Steam distillation**	**Heneicosane (13.8), heptacosane (12.7), β-caryophyllene (9.4), linalool (6.7), pentacosane (6.5)**	**not evaluated**	[59]
***E. sanctae-caterinae* Fayed**	**Egypt**	**Aerial parts**	**Hydro-distillation**	**Valencene (16.01), (+) spathulenol (15.41), (-)-caryophyllene oxide (10.50), limonene (7.66)**	**not evaluated**	[74]
***E. sanctae-caterinae* Fayed**	**Egypt**	**Aerial parts**	**Microwave-assisted**	**Butyl hydroxyl toluene (25.58), β-eudesmol (13.67), 6-*epi*-shyobunol (11.83), (+) spathulenol (10.32), thymol (7.00)**	**not evaluated**	[74]
***E. teheranica* Boiss.**	**Iran**	**Aerial parts**	**Hydro-distillation**	**Elemol (57.5), β-caryophyllene (8.1%), caryophyllene oxide (7.8%)**	**not evaluated**	[75]
***E. thymifolia* L.**	**India**	**Aerial parts**	**Steam distillation**	**Palmitic acid (39.03), phytol (10.367), myristic acid (6.58)**	**not evaluated**	[76]
***E. tithymaloides* L.**	**Bangladesh**	**Aerial parts**	**Steam distillation**	**Eugenol (22.52), phenyl ethyl alcohol (14.63), 3-pentanol (9.22), caryophyllene oxide (7.73), isoeugenol (7.32), pentadecanol (5.14), spathulenol (5.11)**	**Radical scavenging activity (DPPH IC_{50} = 13.67 µg/mL) higher than BHA (IC_{50} = 19.26 µg/mL)**	[77]

The **Table 1** data show that EOs were obtained mainly from aerial parts (39%) and inflorescences (29%), in addition to leaves (18%), roots (11%), and stems (3%), by using basically two extraction methods—hydro-distillation (HD) (52%) and steam distillation (SD) (45%). The oil yield ranged from 0.07% to 1.52% (*v*/*w*) in *E. cotinifolia* (syn. *E. caracasana*) and *E. fischeriana*, and from 0.08% to 0.84% (*w*/*w*) in *E. pilosa* and *E. densa*. Microwave-assisted extraction (MAE) was reported only once (3%) with faster extraction time (3:1) and higher oil yield (1.29% vs. 0.77% *w*/*v*) than conventional techniques (MAE vs. HD) [74]. Qualitative and quantitative analyses were performed by gas chromatography (GC) or GC coupled to mass spectrometry (GC-MS). Samples were found to contain from 8 to 83 phytochemicals representing 81.7–99.9% of the oils content. Oxygenated sesquiterpenes (up to 86.1% of the oil in *E. teheranica*) characterize EOs of *Euphorbia* species, followed by sesquiterpene hydrocarbons (up to 81.4% in *E. helioscopia*) (**Table 1**). In general, *β*-caryophyllene was the most ubiquitous sesquiterpene present in 50% of the species investigated namely in *E. acanthothamnos*, *E. apios*, *E. cotinifolia, E. densa, E. fischeriana, E. fragifera*, *E. golondrina*, *E. helioscopia, E. heterophylla, E. rigida*, *E. sanctae-caterinae*, *E. teheranica* and *E. tithymaloides* constituting more than 7% of their EOs (**Table 1**; **Figure 1**).

[a] Compounds with content higher than 5%.

As reported by Lokar et al. [63], different habitats can influence the quantitative composition of EO from the same species. For example, EO of *E. fragifera* growing in a xeric habitat was richer in aromatic terpenes than that obtained from plants collected in shady and moist soils (e.g., 61.55% vs. 3.36% of carvacrol) being the last ones characterized by great

quantity of acyclic compounds (e.g., 1.24% vs. 59.65% of geraniol). Moreover, variation in the components of EOs may occur due to the season, geographical area, and date of collection [63].

From **Table 1**, it appears that most of the EOs of *Euphorbia* species studied exhibit antioxidant properties, especially by the radical scavenging mechanism. Note that some of them are more active than ascorbic acid, BHT, or BHA compounds well known for their antioxidant properties and are widely used in the food industry as a preservative.

On the other hand, the data presented also show that there are many *Euphorbia* species whose EOs are still not yet studied, thus evidencing a knowledge gap about the potential of these species.

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