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A review of the ethnomedical uses, phytochemistry and pharmacology of the *Euphorbia* genus

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Abstract
The genus *Euphorbia* (spurges, Euphorbiaceae) is the third largest genus of flowering plants, with almost 2000 species. These species was distributed throughout the world. Uses of the plants to treat diseases vary according to the population. In India, many species of *Euphorbia* are used in the treatment of asthma and respiratory tract inflammations. Moreover, especially in Angola, some species of spurges are used against diarrhea, skin ailments, gonorrhea, tumours, asthma, coughs, and dysentery. Phytochemistry studies showed that the *Euphorbia* genus contain mainly, triterpenoids, diterpenoids, flavonoids, tannin and polyphenol. The investigation of biological activity of these compounds sowed different response according to the molecules extract. Many diterpenoids know to have cytotoxicity and anticancer activity. The tripernoids and flavonoids of *Euphorbia* genus were useful to treat the anti-inflammation and inhibition of virus replication.

Keywords: *Euphorbia*, Euphorbiaceae, Phytochemistry, Cytotoxicity, Pharmacological activities.

1. Introduction
Medicinal herbs are the local heritage with global importance. They are used to treat several diseases of humans and animals. Among these herbs, we have the species of *Euphorbia* (Spurges). He is a very large and diverse genus of flowering plants in the spurge family (Euphorbiaceae) [1]. All spurge produce mostly white latex which they exude when cut, and this sap is often toxic. The rich morphological variability and near-cosmopolitan distribution of *Euphorbia* [2, 3] have attracted human interest around the world since ancient and even prehistoric times [4, 5].
Since then, we note a large use of several species of spurge. In Nigeria for example extracts or exudates of the plant are used as ear drops and in the treatment of boils, sore and promoting wound healing [6, 7]. Spurges are known for their uses as ornamental and household plants (*E. milii Des Moul.*, *E. tirucalli* L., *E. lacteal* Roxb.) and their latex contributed to the economic importance of some species such as *Euphorbia antisyphilitica* Zucc. (candelilla wax) [4, 5, 8].
Numerous studies were done on many species of *Euphorbia* to provide phytochemistry and biological activity of the compounds. But until the knowledge is very distributed and don't facility these use to really understand. The aim objective of this study is to provide a summary of the knowledge on the spurges in the world. Especially, we will give the overview knowledge on the ethnomedical uses of *Euphorbia L*, the phytochemistry and the biological activities of the compounds which were isolated.

2. Methodology
To investigate the ethnomedical uses, phytochemistry and pharmacology of the *Euphorbia* genus, we made an extensive literature search. Many of the search term used are: *Euphorbia* and taxonomy, ethnomedical uses of *Euphorbia*, phytochemistry and pharmacology of *Euphorbia* genus. The searches terms yielded more than 200 (by September 2016) mostly English-language publications (besides French) accessible online. They were read and systematically summarize and organize into many titles to facilitate the understanding.

3. Taxonomy
Euphorbia is a very large and diverse genus of flowering plants in the spurge family (Euphorbiaceae) [3]. It contains at least 2,000 species [9]. The scientific classification is:
Kingdom: Plantae
Subkingdom : Tracheobionta

Superdivision	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Suclass	:	Rosidae
Oder	:	Euphorbiales
Family	:	Euphorbiaceae
Genus	:	*Euphorbia*

Extensive phylogenetic studies have supported recognition of four major subgeneric clades: Athymalus (150 spp); Chamaesyce (600 spp); Esula (480spp) and *Euphorbia* (> 600 spp) [2, 5, 10-14].

4. Distribution

The genus *Euphorbia* features several species, distributed throughout in the whole world. Certain species are found in India, more precisely in the North and West [7, 15]. This genus is meeting in West and East Africa where is used in the traditional way by the population to treat various diseases. It is seen in Europe and America.

5. Description and Morphology

The plants are annual or perennial herbs, woody shrubs, or trees with a caustic, poisonous milky latex [9]. The roots are fine or thick and fleshy or tuberous. Many species are more or less succulent, thorny, or unarmed. The main stem and mostly also the side arms of the succulent species are thick and fleshy, 15–91 cm (6–36 in) tall. The deciduous leaves may be opposite, alternate, or in whorls. In succulent species, the leaves are mostly small and short-lived. The stipules are mostly small, partly transformed into spines or glands, or missing [1].

All flowers in the Euphorbiaceae are unisexual, and they are often very small in size. In *Euphorbia*, the flowers are reduced even more and then aggregated into an inflorescence or cluster of flowers known as a "cyathium" (plural cyathia). This feature is present in every species of the genus but nowhere else in the plant kingdom. Whereas most other large genera of plants differ in features of the flowers themselves, *Euphorbia* varies instead in features of the cyathium, which can show amazing modifications in different groups within the genus [16].

Members of *Euphorbia* are readily distinguishable by their milky latex and specialized inflorescences (cyathia) [2, 5, 17]. The main defining feature of the cyathium is the floral envelope or involucre that surrounds each group of flowers. The involucre almost always has one or more special glands attached to it, most often on the upper rim, and these glands and their appendages vary greatly in size and shape. There may be specialized leaves called cyathophylls or cyathial leaves that surround the cyathium and give an overall flower-like appearance to the whole complex inflorescence.

Fig 1[1]: Flower of *Euphorbia milii*

Figure 2[7]: View of *Euphorbia hirta L*

6. Ethnomedical uses

Some species of *Euphorbia* have been used in traditional medicine since many decades in the worldwide to treat a variety of human and animal diseases. Recent studies have shown that more than 5% of species of *Euphorbia* are used in medicine [5]. They are most often used to treat digestive disorders, skin diseases, inflammation and disorders of the respiratory system. Numerous studies referred to the purgative and emetic effect of *Euphorbia* species [18].

Uses of *E. hirta* were very diverse from all over the world, as well as from different plant parts used (latex, entire plant, leaves, stems, roots).Uses was recorded from all continents, except Australasia. In India for example, it is used to treat worm infestations in children and for dysentery, gonorrhea, jaundice, pimples, digestive problems and tumours [7, 19]. A decoction of leafy stems of *E. hirta* is given as anti-diarrheal in Burundi; China; Nigeria and also used for the same purpose in the Philippines [20].

Many species of *Euphorbia* are also used to treat Skin or subcutaneous cellular tissue disorders. The most frequently treated disorders in the category skin diseases were warts, sores, carbuncles, boils, dermatitis, calluses, hair loss, irritation, psoriasis, pustules, sunburn, eczema and the use of *Euphorbia* spp. as astringents. The milky sap or latex of spurges is used to have a protective and defensive role in helping heal wounds [21].

Numerous Scientifics records bring up to the use of *Euphorbia* to treat wounds and hemorrhages. The treatment of abscesses, blisters, burns and injuries were also recorded. In China, both *E. thymifolia* and *E. maculata* are used for the treatment of hemoptysis, hematuria, hemafecia, hematemesis, epistaxis and vaginal bleeding and for the treatment of wounds and carbuncles [18, 20].

In the category of respiratory system disorders, *Euphorbia* was described to treat asthma and coughs, but also included descriptions of treatments for bronchial complaints, breathlessness, pneumonia and use as an expectorant and originating. The most cited species was *E. hirta* [5].

Euphorbia is reportedly used for a multitude of purposes besides medicine and poisons. *Euphorbia* uses described included environmental and ornamental uses (e.g. the well-known house plants poinsettia, *E. pulcherrima* and crown of thorns, *E. milii*) or the usage of *E. tirucalli* and other species, mainly in Africa, to build natural fences [21].

7. Phytochemistry

Many studies have been conducted on the chemical analysis of *Euphorbia* species. The results showed that there are many

chemical molecules. The most encountered are the diterpenoids, the triterpenoids, sterols, flavonoids, phenols and tannins. Zare *et al* (2015) [22] obtained from extracts of *E. macrostegia* three triterpenoids: 24-methylenecycloartan-3β-ol (1) butyrospermol (2) and cycloartenol (3); Three diglycerides, 1,2-Di-O-α-linolenoyl-sn-glycerol (4), 1-O-linoleoyl-3-O-palmitoyl-sn-glycerol (5) and 1-O-α-linolenoyl-2 -O-palmitoyl-sn-glycerol (6) (Figure 3 and 4). Several other compounds were obtained from *Euphorbia* species. These are flavonoids and phenols [3] and diterpenoids (casbane, lathyrane, jatrophane, tigliane, ingenane skeletons) [23].

The study of the chemical composition of the roots of some species of *Euphorbia* helped insulate get diterpenoids whose structures were elucidated as follows: 2α-O-isobutyryl-3β, 5α, 7β, 10, 15 βpenta -O-acetyl-14α-O-benzoyl-10,18-dihydromyrsinol (1), 2α-O-isobutyryl-3β-O-propionyl-5α, 7β, 10,15β-tetra-O-acetyl-10,18- dihydromyrsinol (2) and 2α, 14α-di-O-benzoyl-3β, 5α, 7β, 10,15β-penta-O-acetyl-10,18-dihydromyrsinol (3) [24]. The following table summarizes some components obtained after analysis of some species of *Euphorbia*.

Table 1: Phytochemical constituents of many species of genus *Euphorbia*.

Chemical constituent	Species	References
cycloart-25-ene-3β, 24-diol cycloart-23(Z)- ene-3β, 25-diol cycloart-23(E)-ene-3β, 25-diol 24-methylene-cycloart-3β-ol	*E. macrostegia*	[25]
Phenolic, flavonoid	*E. spinidens*	[3]
Triterpenoids, diglycerides	*E. macrostegia*	[22]
2*α*-*O*-isobutyryl-3*β*,5*α*,7*β*,10,15*β*- penta-*O*-acetyl-14*α*-*O*-benzoyl-10,18-dihydromyrsinol 2*α*-*O*-isobutyryl-3*β*-*O*-propionyl- 5*α*,7*β*,10,15*β*-tetra-*O*-acetyl-10,18-dihydromyrsinol 2*α*,14*α*-di-*O*-benzoyl- 3*β*,5*α*,7*β*,10,15*β*-penta-*O*-acetyl-10,18-dihydromyrsinol	*E. prolifera*	[24]
Euphorbianin, leucocyanidol, camphol, quercitrin and quercitol Gallic acid, myricitrin, 3,4-di-O-galloylquinic acid,2,4,6-tri-O-galloyl-Dglucose, 1, 2,3, 4, 6-penta-O-galloyl-β- D-glucose Euphorbins A, B, C, D, E	*E. hirta*	[7]
Jatrophanes	*E. helioscopia*	[26]
jatrophane diterpene	*E. characias*	[27]
tigliane diterpenes: 16-angeloyloxy-13α-isobutanoyloxy-4β,9α,20-trihydroxytiglia-1,5-diene-3,7-dione 16-angeloyloxy-13α-isobutanoyloxy-4β,9α,7β-trihydroxytiglia-1,5-dien-3-one	*E. grandicornis*	[28]
Triterpenoids: lup-20(29)-ene-33, 28 diol (3β,23E)-Cycloarta-23-ene-3, 25-diol.	*E. spinidens*	[29]

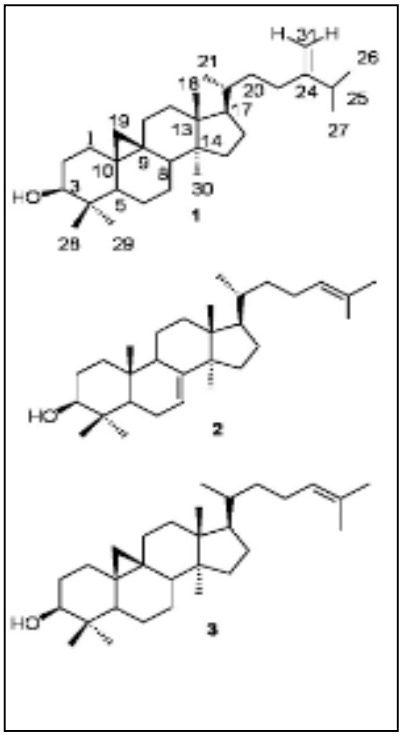

Fig 3: The chemical structure of triterpenoids isolated from *E. macrostegia* (1-3) [22].

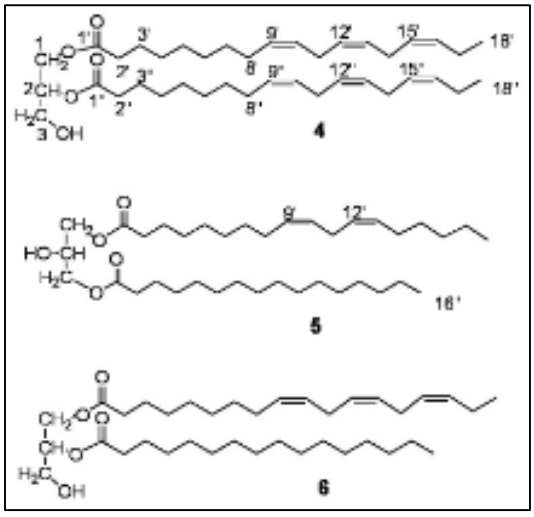

Fig 4: The structure of diglycerides (4-6) [22].

8. Pharmacological activities

a. Neuroprotective activity

Investigations of methane extracts of *E. prolifera* roots have been performed by some chemists. Xu *et al*. (2012) [24] obtained three myrsinolditerpenes which 2α-O-isobutyryl-3β, 5α, 7β, 10,15β-penta-O-acetyl-14α-O-benzoyl-dihydromyrsinol 10.18 (1), 2α-O-isobutyryl-3β-O-propionyl-5α, 7β, 10,15β-tetra-O-acetyl-10,18-dihydromyrsinol (2) and

2α, 14α-di-O-benzoyl-3β, 5α, 7β, 10,15β-penta-O-acetyl-10,18-dihydromyrsinol (3).
Biological evaluation disclosed that two of them exhibited strong neuroprotective effects. The results suggest that myrsinolditerpenes with strong neuroprotective activities may probably be useful for the treatment of nervous system diseases, such as Parkinson's disease [24, 30].

b. Immunomodulatory activity
According to Ghannadian *et al*., 2013 [29], the dried aceton-chloroform extract of aerial parts of *E. spinidens* showed two new triterpenoids: lup-20(29)-ene-33, 28 diol commonly known as betulin and (3β, 23E)-Cycloarta-23-ene-3,25-diol. The pharmacological activity of the two triterpenoids, in particular, betulin showed that they have the immunomodulatory activity. Betulin has shown encouraging stimulatory effect on the proliferation of human peripheral blood lymphocytes activated by PHA.

c. Cytotoxicity activity
Baniadam *et al*., (2014) [25] studied the cytotoxicity of dichloromethane extract of *E. macrostegia* against MDA-MB48 and MCF-7 Cancer Cell Lines. The result showed four compounds: cycloart-25-ene-3β, 24-diol (1), cycloart-23(Z)-ene-3β, 25-diol (2), cycloart-23(E)-ene-3β, 25-diol (3), and 24-methylene-cycloart-3β-ol (4).
Among these compounds, cycloart-23(E)-ene-3β, 25-diol (3) was the most active compound on MDA-MB468 cell line and cycloart-23(Z)-ene-3β, 25-diol (2) was the most active compound on MCF-7 cell line.

d. Antimicrobial activity
Sudhakar *et al*., (2006) [31] evaluated the ethanolic extract of aerial parts of *E. hirta* on some pathogens bacteria. The result showed that the extract exhibited a broad spectrum of antimicrobial activity, particularly against *Escherichia coli* (enteropathogen), *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Staphylococcus aureus.*

e. Antioxidant and antiviral activity
The investigation of methanolic extract of aerial parts of *E. spinidens* was performed for its antioxidant and antiviral activity [3]. The findings of this study show that the methanol extract of *E. spinidens* has high content of phenolic and flavonoid compounds with good antioxidant activity. Furthermore, this extract has significant antiviral effect on HSV-1 probably due to the inhibition of viral replication.

f. Anthelmintic activity
The anthelmintic efficacy of the aqueous crude extract of *E. hirta* Linn was studied in 20 Nigerian dogs that were naturally infected with nematodes. Results of this study show that the aqueous crude extracts of *E. hirta* after its administration into local dogs produced a significant increase ($P< 0.05$) in PCV, RBC, Hb conc., TWBC and lymphocyte counts. The fecal egg counts also showed a remarkable and significant reduction in the levels of the identified helminthes [7, 32].

g. Other activities
Prostratin (a tigliane), which is produced by *E. fischeriana*, and *E. cornigera*, has shown potential as an adjuvant therapy for the treatment of latent HIV infection [23, 33, 34, 35, 36]. An aqueous extract of *E. hirta* significantly inhibited aflatoxin production on rice, wheat, maize and groundnut [7, 37]. The jatrophane esters, which are produced by many species of *Euphorbia*, have been shown to inhibit p-glycoprotein transporters responsible for efflux of chemotherapeutic agents and may therefore be useful for the treatment of multidrug resistant cancers [38, 39, 40].

h. Toxicological evaluation
The spurges share the feature of having a poisonous, milky, white, latex-like sap. The skin-irritating and caustic effects are largely caused by varying amounts of diterpenes. Triterpenes such as betulin and corresponding esters are other major components of the latex [1]. In contact with mucous membranes (eyes, nose, mouth), the latex can produce extremely painful inflammation.
When large succulent spurges in a greenhouse are cut, vapours can cause irritation to the eyes and throat several metres away. Precautions, including sufficient ventilation, are required. Many spurges have also a negative effect on the fertility when they use it at a high level. Certain studies showed that *E. hirta* at a dose level of 50 mg/kg body weight reduced the sperm motility and density of cauda epididymal and testis sperm suspension significantly, leading eventually to 100% infertility [7, 41].

9. Conclusion
In summary, the *Euphorbia* genus consists of several species distributed around the world. The different species of *Euphorbia* have long been used to treat various diseases. The exceptional diversity of the genus *Euphorbia* is not only represented by its growth forms but also by its diverse medicinal uses. These different traditional uses very early attracted the attention of researchers on the need to investigate the different species of spurge. This enabled the isolation of chemical compounds and evaluates together their biological activity. However, it appears necessary to continue the investigations to explore all *Euphorbia* species to find new molecules to face the various common diseases of society.

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