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Formulation evolution and pharmacological properties of *Euphorbia hirta*

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Abstract

Euphorbia hirta, commonly known as asthma weed or garden spurge, is a plant species that has garnered significant attention due to its rich pharmacological properties and traditional uses in various cultures. Belonging to the Euphorbiaceae family, *E. hirta* has been the subject of numerous studies exploring its formulation, evolution, and pharmacological potential. The chemical composition of *Euphorbia hirta* is diverse and includes alkaloids, glycosides, flavonoids, tannins, saponins, and phenolic compounds. These bioactive constituents contribute to the plant's medicinal properties, making it a valuable resource in traditional medicine and modern pharmacology. The formulation of *Euphorbia hirta* extracts and derivatives has been a focal point of research, with various extraction methods such as solvent extraction, distillation, and chromatography being employed to isolate and concentrate its bioactive compounds. The evolution of *Euphorbia hirta*'s pharmacological properties has been a dynamic field of study, with research revealing its potential in diverse therapeutic areas. Studies have demonstrated the plant's anti-inflammatory, antimicrobial, antioxidant, and anticancer activities.

Keywords: Phytochemical diversity, medicinal properties, antibacterial activity, anti-diabetes activity, anti-asthmatic activity

Introduction

Euphorbia hirta linn. Is commonly known as milkweed (Dudhy) and an asthma plant. It is known by the different names in different parts of the world. The plant is characterized by the presence of milky white latex, which is more or less toxic. Latices of E. ingens, E. tirucalli, E. mey, and E. triangularis are possible sources of rubber ^[1]. The roots have long been used in various traditional medicine systems to treat various ailments. Roots of R. communis have diuretic, anticancer, anti-inflammatory, anthelmintic, hepatoprotective, antibacterial, and antispasmodic A combined decoction of R. communis root and Gokhuru (Tribulus terrestris Linn.) with common salty can reduce kidney stones. Roots of R. communis contains saponins (lupeol and erandone), steroidal ester (ricinusterryl benzoate), phenolic compound (ricipentatriacontanol), flavonoids 486 (rutin, quercetin, isoquercetin, and kaempferol), and fatty acid esters (indole-3-acetic acid, 1-Oleio- 2-palmitoglyceryl phosphate)^[2]. Dengue fever is one of the severe health problems during the monsoon periods in India. It is a vector-borne disease transmitted by silent, female urban mosquitoes primarily of Aedes aegypti and Aedes albopictus. The disease spread to tropical and subtropical regions of the world, and 3.9 billion people inhabiting 128 countries are at risk. World Health Organization (WHO) classifies dengue as one of the 17 neglected tropical diseases. Symptoms of dengue start from the 5th d of the bite by an infected mosquito and the symptoms may last for a week or longer. It is selflimiting and characterized by high fever, headache, muscle and joint pain, skin rashes, pain behind the eyes, vomiting, and bleeding from the mouth and nose ^[3]. Use of plants in health care system has been documented since ancient times in different traditional writings including Ayurveda, Unani and Sidhha. Many plants have been successfully used in treatment of various disorders like Catharanthus roseus (vincristine and vinblastine) for cancer, Taxus brevifolia (taxol) for cancer, Cinchona sp. (quinine) for malaria, Digitalis lanata (digoxin) for heart disease, Withania somnifera (withanolides) for cancer and parkinson's disease, Berberis vulgaris (berberine) for antidiabetic ^[4]. There are several published reports describing the antimicrobial activity of various crude plant extracts. It is estimated that there are about 2.5 million species of higher plants and the majority of these have not yet been examined for their pharmacological activities. Euphorbia hirta L. belongs to the family Euphorbiaceae. It is a small annual herb common to tropical countries. It is usually erect, slender-stemmed;

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spreading up to 80 cm tall, though sometimes it can be seen lying down. The plant is an annual broad-leaved herb that has a hairy stem with many branches from the base to the top ^[5]. Among the risks factors, which lead to the mortality and disability along the globe, hypertension is one of the strongest candidates in the development of cardiovascular diseases and death. Hypertension has become the main reason of mortality in developing states, as it causes stroke, kidney impairment, atrial fibrillation, congestive heart failure and cognitive loss. Numerous medicines are available in market to cure hypertension, as their extended use and extra-ordinary price produces several adverse effects and results patients' poor compliance and unaffordability ^[6].



Fig 1: Euphorbia hirta

- Flowers: Unisexual, flowering duration is usually throughout the year. Male flowers: Sessile, fringed, linear bracteoles, single stamen, with absent periapt. [Fig no 2].
- **Fruits:** Allomorphic pistillate fruits, yellow, three lobed capsule, three seeded, keeled capsules, containing three brown, four- sided, angular, wrinkled seeds, base truncate, hairy, 1-2mm in diameter [fig no 3].
- Seed: Very small, oblong (0.57 0.70 mm long, 0.065 mg / seed) (Noda *et al.* 1984) slightly wrinkled, four sided pinkish-brown, caruncle absent. [Fig no 4] ^[7].



Fig 2: Flowers



Fig 3: Fruits



Fig 4: Seed

Table 1: Taxonomical Classifications: [8]

Sr. No.	Classification	Scientific name and Common name
1.	Kingdom	Plantae
2.	Subkingdom	Viridiplantae
3.	Division	Tracheophyta
4.	Subdivision	Spermatophytina
5.	Class	Magnoliopsida
6.	Order	Malpighiales
7.	Family	Euphorbiaceae
8.	Genus	Euphorbia
9.	Species	Euphorbia hirta

Morphology

Euphorbia hirta belongs to the plant family Euphorbiaceae and genus *Euphorbia*. It is a slender-stemmed, annual hairy plant with many branches from the base to top, spreading up to 40 cm in height, reddish or purplish in color. Leaves are opposite, elliptic - oblong to oblong- lanceolate, acute or subacute, dark green above; pale beneath, 1- 2.5 cm long, blotched with purple in the middle, and toothed at the edge. The fruits are yellow, three- celled, hairy, keeled capsules, 1-2 mm in diameter, containing three brown, foursided, angular, wrinkled seeds ^[9].

Bioactive Secondary Metabolites from Euphorbia hirta

The methanolic extract of Euphorbia hirta has been identified with ten compounds, including palmitic acid. chloromorpholin4-ium, S-methyl-L-cysteine, nicotinic acid, methyl 14-methylpentadecanoate, 2,3,5-trimethyl-1 Hpyrrole, 5-methyl-1,3-oxazolidin-2-one, 2-amino3-sulfanylpropanoic acid, 17-carboxyheptadec-9- en-1-ylium and 4-amino-4oxobut-2-enoic acid23. Six compounds were identified and isolated from E. hirta leaves: 3,4-di-O-galloylquinic acid, acid, myricitriu, quercitrin, 1,2,3,4,6-penta-Ogallic galloylbeta-D-glucose and 2,4,6-tri-O-galloyl-D-glucose 24. Aerial parts of the plant were identified with quercitrin, 1,3,4,6-tetra-O-galloyl-β-dglucose, afzelin. 2,4,6-tri-Ogalloyl-β-d-glucose, euphorbins A-D^[10].



Fig 5: Chloromorpholin4-ium



Fig 6: Nicotinic acid



Fig 7: Quercitrin



Fig 8: Gallic acid



Fig 9: 2,4,6-tri-O-galloyl-β-d-glucose

Preparation of *E. hirta* Extracts chart by using Maceration Method



Fig 10: The chart indicates the process of solvent extraction ^[11]

Formulation

Formulation of Topical and Oral formulations

Extraction and preparation Ointment Formulation

The powdered aerial parts of each drug (100 g) were extracted in Soxhlet apparatus for 24 h with ethanol, then concentrated and dried under reduced pressure. The extracts were weighed and percentage yields were calculated in w/w. (*E. hirta* 7.44%, *E. alba* 6.5% and *T. procumbens* 6.22%). The semisolid masses of extracts obtained were used as ingredients for 10% ointment preparation. About 10 g of semisolid extract of aerial parts of *E. hirta* was incorporated in to 100 g of simple ointment base BP and 3.33 g each of semisolid extracts of *E. hirta*, *E. alba* and *T. procumbens* were incorporated in to 100 g of simple ointment base BP12. Simple ointment base was used as placebo in control group. Extract ointments were used twice daily to treat different groups of animals ^[12]. **Mouthwash Formulation:** As much as 100 ml of mouthwash was produced for each formulation with *Euphorbia hirta* L. extract as the active substance. The formulations of *Euphorbia hirta* L. mouthwash Propylene glycol was included in the *Euphorbia hirta* L. extract and placed in a glass beaker. It was then raised to 60 C, stirred with a magnetic stirrer at 300 rpm and Tween 80, and sorbitol and aquadest were added. Benzoic acid and sodium benzoate were dissolved in aquadest and added to the solution and stirred with a magnetic stirrer until homogeneous. Subsequently, 100 ml of the sorbitol qs and aquadest ad was stirred until the solution became clear, and Oleum menthae piperitae was added ^[13]. Evolution parameter

- Skin spreadability: 10% ointment, in hydrophilic base, of 95% ethanolic extract of whole plant of *E. hirta* was topically applied, once daily.
- **Oral administration:** 10% w/v suspension of 95% ethanolic extract of whole plant of *Euphorbia hirta* in 2% tragacanth was given orally, once daily, 200 mg/kg BW ^[14].



Fig 11: Mouthwash

Pharmacological properties 1. Antibacterial Activity

The anti-bacterial activity of E. hirta was discovered and proven by using the methanol extract which showed the property against dysentery causing Shigella species in the Vero cell line. The non-cytotoxic concentration of the plant extract was examined for anti-bacterial activity against the various doses of the pathogen. The extracts were thus proved to be non-cytotoxic and effective anti-bacterial agents. The anti-microbial activity was tested using the nystatin and the methanol extract obtained from the leaves of E. hirta and examined on Candida albicans [15]. Antibacterial effect of compounds extracted from Camellia sinensis L. and the methanol extract of Euphorbia hirta L. were studied against dysentery causing Shigella spp. using the Vero cell line. The antibacterial effects of amethanol extract of E. hirta were demonstrated in vitro using species of Shigella. The extract was non-cytotoxic and antibacterial ^[16]. The ability of the plant extracts/ fractions/ compounds to kill or inhibit the growth of pathogenic microorganisms was evaluated by antibacterial activity. It provides the rationale for the selection of potentially bioactive compounds. The antibacterial screening of plant extracts was carried out by agar well diffusion method based on the procedure given by Opoku 2014 and Medini 2014. Screening of antibacterial activity of the plant extract was performed by disc diffusion technique which is highly effective for rapidly growing microorganisms. [17, 28]

2. Antidiabetes Activity

Anti-diabetes mellitus compounds are compounds that are able to inhibit the breakdown of sugar in the blood or inhibit α -glucosidase. In laboratory experiments, diabetes rats can be induced by administration of streptozotocin. Glibenclamide and acarbose are standard drugs used as anti-diabetics. Oral administration of *E. hirta* extract at a dose of *E. hirta* (400 mg/kg b. wt) in a group of diabetic rats reduced blood sugar levels in streptozotocin-induced diabetic rats. Reduction in blood sugar can be seen from the 7th day after continuous administration of the extract. The effect of *E. hirta* extract on diabetic rats also showed a significant decrease in total cholesterol, low density lipoprotein (LDL) cholesterol, and very low density lipoprotein (VLDL) cholesterol increase in high density lipoprotein (HDL) cholesterol in diabetic rats. ^[18] The ethanol extract of *Euphorbia hirta* showed a significant decreased blood glucose level on alloxaninduced diabetic rats. The antidiabetic effect of ethanolic extract of leaf, flower and stem of *Euphorbia hirta* was investigated in streptozotocin induced diabetic mice. Oral administration of all extracts induced significant reduction in blood glucose level at the 15th day of the study. Ethanol extract and ethylacetate fractions showed α -glucosidase inhibition activity. Based on the *in vitro* and *in vivo* test, *Euphorbia hirta* ethanolic extract and ethyl acetate anti-diabetes mechanism was related to its antioxidant capacity and to α glucosidase inhibitory properties [19].

3. 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 ^[20].

4. Antioxidant: Activity Antioxidants are those substances that shield cells from the dangerous goods of free revolutionaries. Antioxidants may have a circular impact on several degenerative conditions, including cancer and heart complaint since free revolutionaries are constantly linked to these conditions Neelesh Sharma et al. 2014 assessed the antiinflammatory, antioxidant, and anti-cancer goods of the ethanolic excerpt for E. hirta. The exertion of DPPH radical scavenging was assessed with an ESR spectrometer. The DPPH-scavenging exertion of the E. hirta ethanol excerpt 0.5 mg/ml was 61.18 ± 0.22 , whereas the ascorbic acid positive control [0.4mg/ml] demonstrated 100 ±0.22% activity. The antioxidant exertion of E. hirta leaves, stems, roots, and flowers has been delved by Aziana Ismail et al. in 2019. The total phenolic content, flavonoid content, and in-vitro antioxidant exertion of the methanolic excerpt of E. hirta were assessed using the DPPH assay and the methanolic excerpt of E. hirta demonstrated 99.77±0.16 P. [21] The methanol and water extracts of E. hirta showed Huang et al. 5181 antioxidant activities comparable to that of green and black teas. Sharma and Prasad, (2008) has evaluated the antioxidant effects of phenolic acids from aqueous leaf extracts of E. hirta in 2008. To ascertain the efficacy of phenolic acids (mainly hydroxyl cinnamic acid derivatives) to scavenge free radical and antioxidant potential, 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging and FRAP assays were performed [22].

5. Antiasthmatic activity: *E. hirta* is reported to have an antiasthmatic activity due to the relaxation effect on the bronchial tubes and a depressant action on respiration ^[23] Effect of *Euphorbia hirta* against asthmatic rats shows curative property. Ultimately it reduces the levels of WBC's (neutrophils, basophils and eosinophils) that are increased as a result of inflammatory response. Furthermore, review shows that it acts on the dense fibrin network and render it into a fragile form. It is reported as a bronchial tubes relaxant property due to the presence of the flavonoid and Quercitrin ^[24].

6. Antifertility activity: *Euphorbia 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 ^[25].

Toxicology

Euphorbia hirta has been used in folklore medicine from ancient time. The research investigations of the toxicity and safety evaluations of the plant have been lacking, and only a few reports of target organ toxicity or side effects have been cited in previous literature. The water extracts were administrated orally to a 38- week old mature male at the dose of 400 mg/kg to show the activity of the decoctions on the male reproductive organs. ^[26]. The efficacy of binary and tertiary combinations of Euphorbia hirta latex powder with other active compounds like rutin, ellagic acids, teraxerol and betulin. Toxic effect of Euphorbia hirta latex and active compounds were evaluated against fresh water snails Lymnaea (Radux) acuminate and Indoplanorbis exustus in pond. Along with snails, fresh water fish channa punctatus (Bloch) was also lethal to high dose, while LC does not have apparent killing properties in fish populations^[27].

Conclusion

Euphorbia hirta L. emerges as a promising botanical resource with diverse pharmacological properties and medicinal applications. Through comprehensive research, it has demonstrated effectiveness in addressing various health concerns, including bacterial infections, diabetes, asthma, and fertility issues. The identification of bioactive secondary metabolites within Euphorbia hirta provides valuable insights into its mechanisms of action and therapeutic potential. Formulations such as ointments and mouthwashes offer practical and accessible means of administration, further enhancing its utility in healthcare interventions. However, while its therapeutic benefits are evident, further studies are warranted to elucidate its toxicity profile and potential side effects. Moving forward, future research endeavors should focus on clinical validation, exploring synergistic effects with other compounds, and elucidating additional therapeutic mechanisms. By harnessing the pharmacological potential of Euphorbia hirta, we can pave the way for novel treatment modalities and contribute to improved healthcare outcomes worldwide.

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