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Research Article

Anti-inflammatory property of *Euphorbia hirta* L. (Euphorbiaceae) extract as a function of anti-COVID-19 potential

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Abstract

Euphorbia hirta L. (Euphorbiaceae), commonly called 'asthma plant', is a medicinal plant used extensively in traditional medicine for treating bronchial and respiratory diseases (asthma, bronchitis, and hay fever), gastrointestinal and inflammatory disorders. Recent evidence revealed the plant as a major component of an herbal formulation used by the traditional health practitioners in Southeastern Nigeria for the treatment of COVID-19 infection. Inflammation of the airways, and the resulting difficulty in breathing, are known to be associated with COVID-19. The purpose of this study was to investigate the anti-inflammatory activities of *E. hirta* extracts as a function of its potential anti-COVID-19 activity. The anti-inflammatory activity was evaluated using the carrageenan and egg albumin-induced rat paw oedema models respectively. The E. hirta extracts (400 mg/Kg) significantly inhibited both phases of inflammation in the carrageenan and egg-albumin models, with the ethyl acetate fraction exhibiting 53.66 % and 56.09 %, respectively in the 4th hour relative to the standard drug, which gave 46.34 %. The anti-inflammatory activity of *E. hirta,* evidence of its efficacy against asthma and COVID-19, and the involvement of similar inflammatory mediators in both asthma and COVID-19 portray the plant as a potential source of anti-COVID-19 compounds.

1. Introduction

Euphorbia hirta L. (family: Euphorbiaceae), popularly known as 'Asthma Plant' or Spurge, is a small annual herb or weed used widely in traditional medicine for treating bronchial and respiratory diseases (asthma, bronchitis, and hay fever), gastrointestinal and inflammatory disorders. This plant derives its common name, asthma plant, from its anti-asthmatic activity due to the relaxation effect it has on the bronchial tubes and a depressant action on respiration. It is a small, erect or ascending annual herb reaching up to 50 cm, with hairy stems (Fig.1) and exudes a milky white latex or sap when stems or leaves are cut, hence also known as Dove Milk [1]. It is believed to have originated from the Central America but is widespread across the warm, wet tropical and sub-tropical areas of Africa, Australia, northern territory of Queensland, New South Wales, Central America, Indo-Malaysia, Philippines, China and India. [1]. In

Nigeria, it grows wild as a weed in farmlands, waste places along the roadsides and on lawns and is known by its local names in various Nigerian languages as *Nonan Kurchiya* (Hausa), *Udani* (Igbo) and *Akun Esan* or *Ewe Egele* (Yoruba) [1].

E. hirta is used in traditional medicine to treat several conditions, such as hay fever, asthma, worm infestations, bronchial disease, kidney stones, and bowel disease [2, 3]. The plant is a handy first-aid treatment as tea for people experiencing dry cough, respiratory failure, fever and diarrhea which are some of the symptoms of COVID-19 infection. Using the plant thus helps the patients to breathe with ease and removes the need for a ventilator in most cases [1]. Traditionally in Nigeria, a handful of the fresh leaves boiled in 1 litre of water and taken as tea for 2-3 times daily, softens dry cough to release mucus as phlegm, which will clear airways and nasal chambers experienced by patients suffering from coronavirus infection or chronic flu. In Benin (Nigeria), the plant is pounded, mixed with palm oil and licked to treat any form of cough, including the one resulting from coronavirus infection [1].

Reports abound on the several pharmacological activities of different solvent extracts of *E. hirta*. A 95 % ethanolic extract of *E. hirta* has been confirmed to exert anti-inflammatory, antioxidant and anxiolytic effects against asthmatic inflammation in neonatal rats [4]. The antioxidant effect was credited to the constituent phenolic compounds as well as 9,12,15-octadecatrien-1-ol and squalene. The anti-oxidant activity of the methanolic extract was further confirmed by Basma *et al*. (2011) [5]. The anti-inflammatory activity of *E. hirta* has been attributed to the constituents of phytol and myristic acid [6], and hydroxymethyl-2-furancarboxaldehyde [7, 8] which has previously been reported to possess hepatoprotective properties [9]. The 9,12,15-octadecatrien-1-ol, a major constituent of the plant, has been reported with bactericidal action against *Staphylococcus aureus* [10]. The wound healing property of *E. hirta* in alloxan-induced diabetic rats has also been reported [11].

The various phytochemical constituents of *E. hirta* have been reported by several researchers. Quercitrin, isoquercitrin and myricitin are the main flavonoids that have been isolated from the plant. Several tannins, including dehydroellagitannins, euphorbin A, its isomer (euphorbin B), and euphorbin E, as well as galloylglucoses: 2,4,6-tri-O-galloyl-D-glucose, 1,3,4,6-tetra-O-galloyl-β-D-glucose, 1,2,3,4,6-penta-O-galloyl-β-D-glucose, geraniin, 5-O-caffeoylquinic acid, 3,4-di-O-galloylquinic acid, gallic acid, ellagic acid and terchebin have also been isolated [12]. The presence of several fatty acids: 9,12,15-octadecatrien-1-ol, pentadecylic acid, ethyl linoleate, 1,2,3-trihydroxybenzene, gamma-tocopherol, 5-hydroxymethyl-2-furancarboxaldehyde, myristic acid, 7,10-octadecadienoic acid methyl ester, phytol, ethyl palmitate, and squalene in *E. hirta* extract has previously been reported [4]. The triterpenoids: α-amerin, β-amyrin, β-amyrin acetate, taraxerone, taxerol, 11α,12α-oxidotaraxerol, and sterols: 8,29 31 cycloarternol, β-sitosterol, campesterol, stigmasterol, cycloarternol, 24-methylene-cycloarternol and euphorbol hexacozonate have also been reported as bioactive components of the n-hexane extract [12].

In the year 2020, traditional medicinal practitioners in the southeastern part of Nigeria developed a very important herbal mixture which proved very potent against the COVID-19 disease and saved the lives of many patients during the pandemic. A major constituent of the herbal mixture was revealed to be *E. hirta.* The activity of this plant against COVID-19 disease, however, has not been validated scientifically. We report herein the anti-inflammatory properties of *E. hirta* as a function of its potential activity against COVID-19 disease.

Figure 1. *Euphorbia hirta* plant

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2. Materials and methods

2.1. Collection and preparation of the plant materials

The aerial parts of *E. hirta* were harvested from farmland in Orba, Udenu Local Government Area of Enugu State, Nigeria, in January 2022, and were identified and authenticated by Mr. Alfred Ozioko of the International Centre for Ethnomedicine and Drug Development (InterCEDD) Nsukka, where a voucher specimen (Voucher no: InterCEDD/171B) was deposited. The plant materials were cleaned, air-dried and pulverized to tiny particles before extraction.

2.2. Solvent extraction

The prepared plant material (300 g) was successively macerated at room 28 °C with 2 L each of n-hexane, ethyl acetate and methanol, and the extracts were filtered and concentrated *in vacuo* in a rotary evaporator at 40 °C to yield 4.2 g (1.4 %), 7.8 g (2.6 %) and 7.3 g (2.43 %) of n-hexane (HE), ethyl acetate (EAE) and methanol (ME) extracts, respectively. A different portion of 300 g of the plant material was exhaustively extracted by cold maceration in 2 L of 90 % aqueous methanol [13, 14] and also concentrated, yielding 21.6 g (7.2 %) of the crude extract (CE).

2.3. Qualitative phytochemical analysis

The plant extracts were analysed for their phytochemical compositions using the standard protocols [15].

2.4. Anti-inflammatory activity study

The carrageenan-induced and the egg-albumin-induced rat paw oedema models respectively [13, 16,] were used for the anti-inflammatory activity study. The volume of oedema, induced by sub-planter injection of carrageenan or egg-albumin, was used as a measure of acute inflammation. Test samples, at a dose range of 100 - 400 mg/kg, were administered orally to each of the animal groups (n = 5). The choice of the dose range was based on previous similar works on plant extracts [13]. Control animals received an equivalent volume of vehicle (3% v/v Tween 80) or 10 mg/kg piroxicam. Thirty minutes after drug administration, inflammation was induced by sub-plantar injection of 0.1 mL of freshly prepared 1 % w/v carrageenan suspension or 0.1 mL of fresh undiluted egg albumin (as the case may be) into the left hind paw of the animals. Oedema volume was measured with plethysmometer before and after 1, 2, 3 and 4 h, respectively after induction of inflammation. The percentage inhibition of oedema was calculated using the standard relation [13].

$$\% \text{ Inhibition} = \frac{[Vt-V0(\text{control})]-[Vt-V0(\text{test})]}{Vt-V0(Control)} \times 100\ \%$$

Where, V_t is the oedema volume of the test sample group at a time, t, and V_0 is the original oedema volume before inflammation.

2.5. Statistical analysis

The results obtained were analysed with one-way ANOVA expressed as mean ± SEM and student *t*-test was used to test the difference between the mean of the treated and the control groups, which were considered significant at $p<0.05$. The software used was GraphPad Prism version 7.0.

3. Results and discussion

The percentage yields of the extracts revealed that the plant has a lower concentration of the n-hexane-soluble phytochemicals (steroids, terpenes and fatty acids) than the moderately polar ethyl acetate-soluble components (mainly alkaloids) and the polar ones (phenolics). The high yield (7.2 %) of the extraction with 90 % aqueous methanol also confirms that the solvent is capable of extracting both polar and non-polar components [13, 14].

The result of the preliminary phytochemical analysis of the aqueous methanol extract of *E. hirta* (Table 1) reveals the presence of alkaloids, saponins, tannins, flavonoids, steroids and terpenoids. These compounds contribute to the various pharmacological activities of *E. hirta*.

Table 1. Qualitative phytochemical composition

Compound classes	HE	EAE	ME	CE
Alkaloid	+	+	-	+
Flavonoid	-	-	+	+
Tannin	-	-	+	+
Saponin	-	-	+	+
Terpenoid	+	+	-	+
Steroid	+	-	-	+

+ Present; - Not detected

One or a combination of these phytoconstituents may be responsible for the observed anti-inflammatory activity. Flavonoids such as quercetin and myricitrin have been reported to induce the anti-inflammatory

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Table 2. Dose dependent inhibitions of the carrageenan-induced rat paw oedema by the crude extract

Group	Dose (mg/kg)	Paw oedema volume ± SEM (mL) (% Inhibition)			
		1 h	2 h	3 h	4 h
1	100	0.50 ± 0.33 (15)	0.51 ± 0.33 (26)	0.49 ± 0.33* (35)	0.48 ± 0.33* (43)
2	200	0.50 ± 0.33 (20)	0.50 ± 0.33 (30.8)	0.48 ± 0.33* (39.7)	0.46 ± 0.33* (54.2)
3	400	0.50 ± 0.33 (25.38)	0.47 ± 0.33* (43)	0.47 ± 0.33* (51.7)	0.44 ± 0.33** (66.4)
4	Diclofenac Na (10 mg/kg)	0.50 ± 0.33 (20.7)	0.50 ± 0.33 (31.6)	0.47 ± 0.33 (47.4)	0.44 ± 0.33 (69)

*Values are significantly different from the negative control at ($p < 0.05$), n = 5

Table 3. Dose dependent inhibitions of the egg albumin-induced rat paw oedema by the crude extract

Group	Dose (mg/kg)	Paw oedema volume ± SEM (mL) (% Inhibition)			
		1 h	2 h	3 h	4 h
1	100	0.52 ± 0.14 (7.1)	0.48 ± 0.14 (14.2)	0.43 ± 0.12 (23.07)	0.42 ± 0.14 (30.7)
2	200	0.52 ± 0.14 (14.3)	0.50 ± 0.14 (21.4)	0.47 ± 0.14* (38.4)	0.44 ± 0.14* (61.5)
3	400	0.53 ± 0.14 (14)	0.52 ± 0.14 (35.7)	0.50 ± 0.14** (69.2)	0.48 ± 0.14** (76.9)
4	Diclofenac Na (10 mg/kg)	0.51 ± 0.14 (21)	0.50 ± 0.14 (28.5)	0.47 ± 0.14 (46.1)	0.42 ± 0.14 (77)

*Values are significantly different from the negative control at ($p< 0.05$), n = 5

and anti-asthmatic effects [17, 18]. Phenolics exert anti-inflammatory effect by regulating cell activity in inflammatory cells and regulating the enzymes implicated in the metabolism of arachidonic acid [19]. Steroids and triterpenoids are known to exert their anti-inflammatory effect by inhibiting phospholipase A2, a key enzyme of arachidonic acid metabolism, hence inhibiting prostaglandin synthesis [20].

The acute inflammation was induced using two different philogistic agents, namely, carrageenan and egg albumin respectively. The time course of oedema development in carrageenan-induced paw oedema and egg albumin induced paw oedema models in rats is represented by a biphasic curve [13]. From the results, the anti-inflammatory activities in both models were more significant at 3rd and 4th h compared to the first two hours. The first phase of inflammation with carrageenan occurs within an hour due to the release of histamine and serotonin, while the egg albumin oedema is mediated by the release of histamine, serotonin and bradykinin [21]. These mediators cause inflammation by increasing vascular permeability in the damaged tissue surroundings. The cyclo-oxygenase involved in prostaglandin synthesis plays a major role in the development of the second phase of inflammation. The result (Tables 2 and 3) showed a dose dependent significant anti-inflammatory effect of the aqueous methanol extract (CE) of *E. hirta*.

The CE showed appreciable activity comparable to the standard reference. The result of the anti-inflammatory effect of *E. hirta* in Table 2 indicates that at 4th hr, CE showed significant percentage inhibition of 43 %, 54.2% and 66.4% for 100 mg/kg, 200 mg/kg and 400 mg/kg doses respectively, while the standard reference (diclofenac) gave 69%. The negative control group, which received Tween 80 showed no significant anti-inflammatory activity.

Using egg albumin induced paw oedema (Table 3), *E. hirta* also showed dose dependent anti-inflammatory activity. At the 4th hour, the plant extract showed significant percentage inhibition of 30.7%, 61.5% and 76.9% for 100 mg/kg, 200 mg/kg and 400 mg/kg doses respectively, while the positive control group gave 77%.

From the results in Tables 2 and 3, the aqueous

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Table 4. Inhibition of the carrageenan-induced oedema by different solvent extracts of *E. hirta*

Group	Extract (mg/kg)	Paw oedema volume ±SEM(mL) (% Inhibition)			
		1 h	2 h	3 h	4 h
1	HE	0.510 ± 0.06[b] (42.6)	0.500 ± 0.00[b] (41.86)	0.460 ± 0.06[b] (45.23)	0.437 ± 0.009[b] (48.78)
2	EAE	0.480 ± 0.06[a] (44.19)	0.450 ± 0.015[a] (48.84)	0.400 ± 0.012[a] (52.38)	0.380 ± 0.012[a] (53.66)
3	ME	0.510 ± 0.06[b] (41.51)	0.510 ± 0.06[b] (39.28)	0.500 ± 0.00[b] (40.48)	0.490 ± 0.006[c] (40.24)
4	Diclofenac Na (10 mg/kg)	0.500 ± 0.06[b] (41.86)	0.493 ± 0.009[b] (41.66)	0.460 ± 0.006[b] (45.24)	0.440 ± 0.012[b] (46.34)

HE: n-hexane fraction; EAE: Ethyl acetate fraction; ME: Methanol fraction

Table 5. Inhibition of the egg albumin-induced oedema by different solvent extracts of *E. hirta*

Group	Extract (mg/kg)	Paw oedema volume ± SEM (mL) (% Inhibition)			
		1 h	2 h	3 h	4 h
1	HE	0.527 ± 0.033 (38.72)	0.510 ± 0.006 (39.29)	0.483 ± 0.009 (42.5)	0.480 ± 0.01 (41.66)
2	EAE	0.450 ± 0.058 (47.67)	0.430 ± 0.012 (48.80)	0.410 ± 0.015 (51.19)	0.360 ± 0.00 (56.09)
3	ME	0.510 ± 0.058 (46.69)	0.500 ± 0.012 (40.48)	0.480 ± 0.012 (42.85)	0.480 ± 0.00 (41.46)
4	Diclofenac Na (10mg/kg)	0.500 ± 0.058 (41.86)	0.493 ± 0.09 (41.66)	0.460 ± 0.006 (45.04)	0.440 ± 0.012 (46.34)

HE: n-hexane fraction; EAE: Ethyl acetate fraction; ME: Methanol fraction

methanol plant extract (CE) of *Euphorbia hirta* showed comparable anti-inflammatory activity with the standard drug, diclofenac. The anti-inflammatory activity is attributed to the inhibition of prostaglandin synthesis [13] by the phytochemical constituents of the *E. hirta* extract.

Recent studies revealed that the carrageenan injection significantly elicits increased levels of CINC-2, CINC-3, IL-1β, IL-6, β-NGF, TNF-α, and VEGF in paw tissue and that of CINC-2 and CINC-3 in serum when compared to control as quantified by ELISA [22]. Similarly, patients with COVID-19 have been reported with significantly higher levels of interleukins 1α, 2, 6, 7, 8, 10 and 15, C-reactive protein (CRP), serum amyloid A (SAA), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1), TNF-α, basic fibroblast growth factor (bFGF), placental growth factor (PlGF), and fms-like tyrosine kinase 1 (Flt-1) [23]. The findings revealed that CRP, SAA, VCAM-1, CXCL10, CCL22 and IL-10 levels are promising biomarkers for COVID-19 disease severity, suggesting that plasma inflammatory mediators could be used as warning indicators of COVID-19 severity, aid in COVID-19 prognosis and treatment [23]. Furthermore, the concentrations of IL-1, TNF-α, IL-6, CXCL8 and CXCL10, and CCL4, CCL11, CCL17, and CCL22 are implicated in asthmatics [24-26].

The ethyl acetate extract of *E. hirta* (EAE) exhibited the best anti-inflammatory activity and contains mainly alkaloids (Tables 1, 4 and 5). This implies that alkaloids are most likely to be responsible for the anti-inflammatory activity of the plant.

4. Conclusions

Euphorbia hirta possesses strong anti-inflammatory activity in the carrageenan and egg albumin oedema models. This property of *E. hirta*, together with evidence of its efficacy against asthma and COVID-19, and the involvement of similar inflammatory mediators in carrageenan-induced inflammation, asthma and COVID-19 disease, portrays the plant as a potential source of anti-COVID-19 compounds.

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Ethical statement

The experimental protocol was in accordance with the guidelines of the ethics committee of the University of Nigeria as registered by the National Health Research Ethics Committee of Nigeria (ref: NHREC/05/01/2008B). The research was conducted in accordance with the internationally accepted principle for laboratory animal use and care as found in European Community Guidelines (EEC Directive of 1986; 86/609/EEC). The ethics for the use of experimental animals were followed carefully.

Authors' contributions

Conceptualization, F.I.E., P.O.O.; Methodology, C.M.A., C.C.C., C.N.C., W.I.U., P.I.D., P.C.O., O.C.O., C.S.O.; Software, F.I.E., C.N.C., P.I.D., C.M.A.; Validation, W.I.U., F.I.E., P.O.O.; Formal analysis, F.I.E., W.I.U.; Writing– original draft and preparation, C.M.A., C.C.C., C.N.C., P.I.D., P.C.O., O.C.O., C.S.O ; Writing – review & editing, F.I.E.; Supervision, F.I.E., P.O.O., W.O.O.; Project administration: F.I.E., P.O.O., W.O.O., W.I.U.; Funding acquisition: F.I.E., C.M.A., C.C.C., C.N.C., W.I.U., P.I.D., P.C.O., O.C.O., C.S.O.

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Availability of data and materials

All relevant data are within the paper and its supporting information files. Additional data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare that there is no conflict of interest in this work.

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