Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating 2017: 3.53
JMPS 2017; 5(3): 170-175

Received: 05-03-2017
Accepted: 06-04-2017

Mohammad Abu Bin Nyeem
Department of Unani Medicine, Hamdard University Bangladesh

Mohammad Sadul Haque
Department of Unani Medicine, Hamdard University Bangladesh

Mohammad Akramuzzaman
Govt. Unani & Ayurvedic Medical College & Hospital, Dhaka, Bangladesh

Rabeya Siddika
Department of Public Health, ASA University Bangladesh

Sanjeeda Sultana
Department of Public Health, ASA University Bangladesh

BM Rabiul Islam
Department of Public Health, ASA University Bangladesh

Correspondence
Mohammad Abu Bin Nyeem
Department of Unani Medicine, Hamdard University Bangladesh

Euphorbia hirta Linn. A wonderful miracle plant of mediterranean region: A review

Mohammad Abu Bin Nyeem, Mohammad Sadul Haque, Mohammad Akramuzzaman, Rabeya Siddika, Sanjeeda Sultana and BM Rabiul Islam

Abstract
Euphorbia hirta L. belonging to the family Euphorbiaceae which is frequently seen occupying open waste spaces and grasslands, road sides, and pathways in many parts of the world. The aim of the present study investigation was carried out to compile the medicinal properties of different plant parts of *E. hirta* L. and to compare their traditional uses with scientific evidences. The leaves of *E. hirta* are found to contain flavonoids, polyphenols, tannins, sterols, alkaloids, glycosides and triterpenoides. The plant has a reputation for increasing milk flow in women because of its milky latex and is used for other female complaints as well as diseases like bronchitis, asthma, eczema, dysentery. It is used as antidiarrheal, antispasmodic, anti-inflammatory, antifungal, anticancer, antimalarial, antiamoebic, antibacterial and antihelmentic etc.

Keywords: *Euphorbia hirta*, Pharmacological activity, Euphorbiaceae

1. Introduction
The genus Euphorbia is the largest genus of medicinal plants widely distributed in most part of the china, India, Bangladesh and Pakistan. *Euphorbia hirta* is an annual herb 15-50cm high, erect or ascending, hispid with long often yellowish crisped hairs; stems usually terete; branches often lanceolate or obovate-lanceolate, acute or subacute, serrulate or dentate, dark green above, pale beneath, base usually unequal sided acute or rounded. It is a common weed found throughout the hotter part of India and most of tropical and subtropical countries [1]. The plants are characterized by the presence of milky latex. The extract of *E. hirta* has sedative effect on the mucous membrane of the respiratory and gentio-urinary tract. The plant has been also used in bowel complaints, worm infestations, kidney stones and low milk yield. The whole plant has also been reported to possess anti-bacterial, anti-amoebic, anti-fungal, anti-viral, spasmolytic, anti-diarrheal, sedative, anxiolytic, analgesic, anti-pyretic, anti-inflammatory, anti-malarial and anti-hypertensive properties.

Fig 1: *Euphorbia hirta*

Phytochemistry
Phytochemistry (the Greek word "Phyto" meaning plant) is the branch of chemistry, deals with chemical nature of the plant or plant products (chemistry of natural products). Phytotherapy acts as a source of treating and improving certain diseases by using the beneficial effects of medicinal plants. Phytochemicals are the bioactive, natural chemical compounds, found in plants. *Euphorbia hirta* contains flavonoids, terpenoids, phenols, essential oil and other compounds [2].

Flavonoids:- Quercetin, quercitrin, quercitol and derivatives containing rhamnose, quercetinrhamnoside, a chlorophenolic acid, rutin, leucocyanidin, leucocyanidol, myricitrin, cyaniding 3,5-diglucoside, pelargonium 3,5-digucoside and camphol, flavonol glycoside xanthrhamnin, hentriacontane, myricyl alcohol, inositol, tetraxerol, friedelin, β-sitosterol, ellagic acid, kaempferol. Terpenoids:- Titerpenoids, α-amyrin, β-amyrin, friedelin, teraxerol, and its esters-taraxerone, 11α, 12α-oxidoteraxerol, cycloartenol, 24-methylene-cycloartenol, euphorbol hexacosonate. Diterpene esters of phorbol type and ingenol type including 12-deoxy phorbol-13dodecanoate – 20-acetate, 12-deoxy phorbol -13-phenyl acetate-20-acetate, ingenol triacetate, higly toxic tinyatoxin, a resiniferonol derivative. 2-beta, 16-α, 19- trihydroxy – ent-kaurane, 16-alpha, 19-dihydroxy-ent-kaurene. Other isolated terpenoids are sterols, including βsitosterol, campestrol, cholesterol and stigmasterol. Tannins:- Dimeric hydrolysable dehydro ellagic tannins, euphorbins A, B, C, E and terchebin, the monomeric hydrolysable tannins geraniin, 2,4,6-tri-o-galloyl-β-D-glucose and 1,2,3,4,6-penta-O-galloyl-β-D-glucose and the esters 5-O-caffeoyl quinic acid (neo chlorogenic acid), 3,4 –di-o-galloyl quinic acid and benzyl gallate.

Acids:- Ellagic, gallic, tannins, maleic and tartaric acids. Essential oil:- Major constituents include 3,7,11,15-tetra methyl-2-hexadecon-1-ol, 6,10,14trimethyl-2-pentadecanone,hexaecanal, phytol and n-hexadecanoic acid. Minor constituents include 2-butoxyethanol, tetradecane, phtalic acid, butyl tetradecyl ester, oleic acid, 13-hepta decyl-1-ol, 2-methyl-1-hexadecanol and 1,2 – benzene dicarboxylic acid diisocylester. Other compounds:- Alkaloids, saponins, amino acid and mineral. Two new compounds nbutyl-1-0-L-rhamno pyranoside and n-butyl-1-0-L-rhamnopyranoside [2].

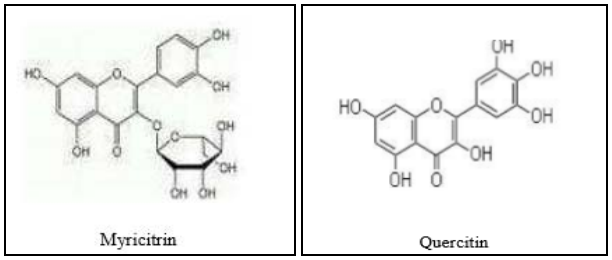

Fig 2: Phytoconstituents of *Euphorbia hirta*

Pharmacological activity

Anti-inflammatory activity

The n-hexane extract of the aerial parts of *E. hirta* and its main constituent triterpenes, β-amyrin, 24methylenecycloartenol, and β-Sitosterol were evaluated for anti-inflammatory effects in mice. Both the extract and the triterpenes exerted significant and dose dependent anti-inflammatory activity in the model of phorbol acetate-induced ear inflammation in mice. The lyophilized aqueous extract showed analgesic, antipyretic and anti-inflammatory activity in mice and rats. A central depressant activity, expressed by a strong sedative effect associated with anxiolytic effect, was also observed [3].

Antidiarrhoeal activity

Forty six aqueous extracts from 38 medicinal plant species belonging to different families were selected on the basis of their traditional medicinal use as antidiarrheal agents. Only 8 plant extracts (17.39%) proved as antidiarrheal agents by a triple pronounced antibacterial, antiamoebic and antispasmodic action. They include aqueous extracts from *Euphorbia hirta* whole plant, leaves of *Psidium guajava* and *Tithonia diversifolia*, root bark of *Alchornea cordifolia, Heinsia pulchella, Paropsia brazzeana, Rauwolfia obscura and Voacanga Africana* [4].

Wound healing activity

The ethanolic extract of whole plant of *E. hirta* possesses significant wound healing activity. The histopathological study, W.B.C. count and haemostatic activity were carried out to support its wound healing activity. The ethanolic extract of *E. hirta* has promoted wound healing activity and probable mechanism may the promotion of collagen biosynthesis which further supports for increase in tensile strength of the granulloma tissue. This evidence supports the use of *E. hirta* in the management of wounds [5].

Anti-tumour activity

Shao-Ming Chi *et al*., 2012 isolated a new cylclopentanone derivative (1'R,5'R)-5-(5'carboxylmethyl-2'-oxocyclopentyl)-3Z-pentenyl acetate from *Euphorbia hirta*. Based on spectroscopic analysis 1D and 2D NMR the structure was elucidated. The cytotoxicity of ethanol extract was evaluated against K562 (human leukemia) and A549 (lung cancer) cell lines. From the data, the ethanol extract exhibited a weak activity against A549 cells (inhibition ratio 15.02 ± 11.60%) and inactive against K562cells [6].

Antitumour activity of *Euphorbia hirta* Linn was studied by Sandeep *et al*., 2011. Aerial parts of the plant, *Euphorbia hirta* were extracted with ethanol, chloroform and petroleum ether. All the extracts showed positive result for tannin, saponin, alkaloids and flavonoids. Chloroform, ethanol extract enhanced mean survival time and reduced solid tumor mass tumour bearing mice. This antitumour activity due to presence of flavonoids [7].

Anti-diabetic and free radical scavenging activity

Goldie Uppal *et al*., 2012 discussed anti-diabetic activity. The ethanol extract of *Euphorbia hirta* Linn was tested using animal screening models. Alloxan administered for 21 days, to induce diabetics. The ethanol extract showed a significant decreased blood glucose level (hypoglycemic effect) on alloxan-induced diabetic rats [8]. *In vivo* and *in vitro* study of antidiabetic activity was done by Widharna *et al*., 2010. From the *in vitro* experiment, ethanol extract and ethylacetate fractions had α-glucosidase inhibition activity, while n-hexane, chloroform, butanol and water fractions had no α-glucosidase inhibitory effect. *In vivo* test, also had the same result. Based on *in vitro* and *in vivo* test, *Euphorbia hirta* L. ethanolic extract and ethylacetate extract exerted anti-diabetic mechanism and α-glucosidase inhibitory property [9].

Anti-allergic activity

Singh *et al*., 2006 described a antiallergic reactions. 95% ethanolic extract prepared from whole aerial parts of *Euphorbia hirta* (EH A001). EH A001 significantly inhibited

rat peritoneal mast cell degranulation triggered by compound 48/80, dextran-induced rat paw edema. It prevented eosinophil accumulation and eosinophil peroxidase activity and reduced the protein content in bronchoalveolar lavage fluid (BALF). Extract suppressed the CD4/CD8 ratio in peripheral blood. It also attenuated interleukin-4(IL-4) release and augmented interleukin –ϒ (IFN- ϒ) in ovalbumin-sensitized mouse splenocytes. The results of these findings compared with ketotifen, cetirizine and cyclophosphamide, known compounds and it proved that *Euphorbia hirta* possessed significant activity to prevent early and late phase allergic reactions [10].

Analgesic and anti-anaphylactic activity

Euphorbia hirta ethanol extract (EH A001) administered orally (100 to 1000mg/kg) against compound 48/80 induced systemic anaphylaxis. The data showed that EH A001 inhibited passive cutaneous anaphylaxis (PCA) in rat and active paw anaphylaxis in mice. The result also showed a suppressive effect on TNF-α and IL-6 release from anti-DNP-HSA activated rat peritoneal mast cells. Thus, Youssouf *et al*., 2007 proved anti-anaphylactic effect of *Euphorbia hirta* [11].

Antioxidant activity

The in-vitro antioxidant activity was carried out to evaluate reducing power, Superoxide anion scavenging activity, hydroxyl radical scavenging activity, nitric oxide radical scavenging activity. The degree of protection was determined by measuring levels of biochemical markers like SGOT, SGPT, ALP, Bilirubin, the histopathological studies were also carried out. Significant increase in GSH level and scavenging activity and decreased lipid peroxidation. The results were comparable with the standard. *In vitro* antioxidant studies were carried out. Administration of alcoholic extract of *Euphorbia hirta* whole plant at 100µg dose has demonstrated dose dependent increase in reducing power, which is comparable to that of std. sodium metabisulphate at 25µg. Similar results are obtained in case of superoxide anion, hydroxyl radical scavenging activity, Nitric oxide radical scavenging activity. Alcoholic extract of *Euphorbia hirta* whole plant has significant *in vitro* lipid peroxidation and scavenging activity among other polar extracts [12].

Anti-asthmatic Activity

Ethanolic extract of *Euphorbia hirta* was evaluated using *in vitro* goat tracheal chain preparation model and Clonidine induced catalepsy in mice model. Histamine induced contraction in isolated goat tracheal chain shows that ethanolic extract of *Euphorbia hirta* inhibited the contractile effect of histamine. Anti-asthmatic activity was increased with the increasing concentration of extract. Presence of Phytochemical like flavonoids, glycosides, saponine might contribute to the observed anti asthmatic activity [13].

Immunostimulant effect

E. hirta leaves have been used in aquaculture to protect fish from bacterial infection. Aquaculture is one of the fastest growing food-producing fields in the world, with an annual average growth rate of 6.9% per year since 1970 and this sector contributed about 36% of the total global fisheries production in the year 2006 [14-15]. Infectious diseases are a major problem in aquaculture, causing heavy loss to fish farmers. Immunostimulants increase resistance to infectious diseases by enhancing both specific and nonspecific defence mechanisms. The use of immunostimulants in fish culture is a promising new development in the field [16-18]. Pseudomonas fluorescens Flügge (Pseudomonadaceae) is an opportunistic bacterial fish pathogen of the freshwater ecosystem, associated with septic and ulcerative condition, necrosis of internal organs, external lesions, loss of pigmentation, and so on [19]. The leaf extracts of *E. hirta* administered through the diet enhanced the nonspecific defense mechanism in terms of increased number of activated neutrophils and enhanced the serum lysozyme activity (secreted from active macrophages) in *Cyprinus carpio* Linn. The immunological competence was developed earlier on the plant leaf extract fed fish (on 5th day) than the control fish (on 10th day) after infection with the pathogen. In addition, the extract also exhibited potent antibacterial activity [20]. Immunostimulatory activity of *E. hirta* was also found to enhance *in vitro* phagocytosis of neutrophils and macrophages [21].

Effects on renal system

Dickshit [22] (1934) first reported the presence of a toxic principle in *E. hirta* that depressed the cardiovascular system with a resulting fall in blood pressure. The alcoholic and aqueous extracts of this plant have also been shown to depress the blood pressure of the dog [23]. *E. hirta* is locally used to treat numerous diseases, including hypertension and edema in Africa [24]. Diuretic effect of the *E. hirta* leaf extracts were assessed in rats using acetazolamide and furosemide as standard diuretic drugs. The water and ethanol extracts (50 and 100 mg/kg) of the plant produced time dependent increase in urine output. Regarding the secretion of electrolytes, the ethanol extract of *E. hirta* increased the excretion of HCO3-, decreased the loss of K+ and had little effect on renal removal of Na+. Whereas, the water extract increased the urine excretion of Na+, K+ and HCO3- that was similar to acetazolamide [25].

The renin–angiotensin system plays a vital role in the maintenance of vascular tone and peripheral resistance. Renin produced from the juxtaglomerular apparatus of the kidney splits angiotensinogen to produce the inactive decapeptide angiotensin I. The latter is then converted to the powerful octapeptide vasoconstrictor, angiotensin II by the action of angiotensin converting enzyme (ACE). ACE inhibitors are important agents for treating hypertension and congestive heart failure [26]. *E. hirta* extract possessed compounds with potent ACE inhibitor activities. A dose of 500 mg crude extract expressed about 90% inhibition of the enzyme action. The study also revealed that the most active ACE inhibitor compounds were present in the medium polar (chloroform extract) and very polar (methanol and water) fractions. Extract of *E. hirta* (10 mg/100 mg body weight) also possessed anti-dipsogenic activities [27]. Both diuresis and ACE inhibition effects of *E. hirta* may explain its antihypertensive effects.

Antibacterial and Antifungal Activity

The antimicrobial activities of the methanolic extracts of *Euphorbia hirta* L leaves, flowers, stems and roots were evaluated against some medically important bacteria and yeast using the agar disc diffusion method. Four Gram positive (Staphylococcus aureus, Micrococcus sp., Bacillus subtilis and Bacillus thuringensis), four Gram negative (Escherichia coli, Klebsiella pneumonia, Salmonella typhi and P. mirabilis) and one yeast (*Candida albicans*) species were screened. Inhibition zones ranged between 16–29 mm. Leaves extract inhibited the growth of all tested microorganisms with large zones of inhibition, followed by that of flowers, which

also inhibited all the bacteria except C. albicans. The most susceptible microbes to all extracts were S. aureus and Micrococcus sp. Root extract displayed larger inhibition zones against Gram positive bacteria than Gram negative bacteria and had larger inhibition zones compared to stem extract. The lowest MIC values were obtained with E. coli and C. albicans (3.12 mg/mL), followed by S. aureus (12.50 mg/mL) and *P. mirabilis* (50.00 mg/mL). All the other bacteria had MIC values of 100.00 mg/mL. Scanning Electron Microscopic (SEM) studies revealed that the cells exposed to leaf extract displayed a rough surface with multiple blends and invaginations which increased with increasing time of treatment, and cells exposed to leaf extract for 36 h showed the most damage, with abundant surface cracks which may be related to final cell collapse and loss of function. Time-kill assay of C. albicans indicated a primarily fungicidal effect at 1- and 2-fold MIC. *E. hirta* extracts had LC50 values of 0.71, 0.66, 0.41 and 0.03 mg/mL for stems, leaves, roots and flowers, respectively against *Artemia salina*. Hence, these plants can be used to discover new bioactive natural products that may serve as leads in the development of new pharmaceuticals [28].

Anti-thrombocytopenic activity

Antithrombocytopenic effect of lyophilized decoction of *Euphorbia hirta* Linn was studied by Jovencio G Apostol in Sprague-Dawley rats. Ethanol induction induced thrombocytopenia within 7days in rats. Platelet count, bleeding time and clotting time were assayed in four groups of rats. A significant increased platelet count decreased bleeding and clotting time observed after *Euphorbia hirta* treatment. Histopathological studies showed a decreased liver sinusoidal dilation in *Euphorbia hirta* treated groups. *Euphorbia hirta* decoction, thus, acts as potential antithrombocytopenic [29].

Sperm motility

Oyeyemi *et al*., 2009 utilized sexually mautured and healthy west African Dwarf (WAD) rams. The rams aged between 24 and 30 months were used for study. Experimental animals were orally dosed with 400mg/kg body weight for 14days. Semen samples were collected after a day and seven days after administration. Semen picture showed a significant reduction ($p<0.05$) of sperm motility from 80% to 47.5% and live – dead ratio from 90.75% to 32.5%. This result indicates that fertilization capacity and livability of spermatozoa were negatively affected. But no significant difference in values of body parameters. Thus *Euphorbia hirta* was not recommended for medicinal purpose in male animals [30].

Genototoxic effect

Kwan Yuet Ping *et al*., 2012 investigated genotoxic effect of methanol extract of *Euphorbia hirta* using *Allium cepa* assay. The extracts 125, 250, 500 and 1000 µg/ml were tested on root meristems of *Allium cepa*. Ethylmethane sulfonate and distilled water served as positive control and negative control. A decreased mitotic index and a increased chromosome aberrations were observed as the concentrations of *Euphorbia hirta* extract increased. Some abnormalities like stickiness, c-mitosis, bridges and vagrant chromosomes were also observed. At interphase stage, micro nucleated cells also observed. This result confirmed that *Euphorbia hirta* methanol extract (1000 µg/ml) exerted a significant genotoxic and mitodepressive effect [31].

Synergistic activity

Michel Adikwu *et al*., 2010 illustrated *in vitro* combined effects of erythromycin and *Euphorbia hirta* leaves methanol extract against staphylococcus aureus using checker board technique. The results indicate that some combination of *Euphorbia hirta* leaf and erythromycin at a given ratio 9:1, 8:2, 6:4, 3:7, 2:8, 1:9 showed synergistic activity, while other ratios 5:5, 4:6 showed indifference [32].

Effect on CNS

Lanhers *et al*., 1996 evaluated lyophilized aqueous extract of *Euphorbia hirta* L. (Eh) for benzodiazepine-like properties, hypnotic, neuroleptic and antidepressant properties. The result showed that aqueous extract does not seem to possess benzodiazepine like properties hypnotic, neuroleptic effect. The plant extract caused a direct action on central nervous system and a slight depressant effect [33].

Anti-malarial activity

Neetu arya *et al*., 2011 isolated mosquito larvicidal bioactive saponin from indigenous plant, *Euphorbia hirta*. The isolated bioactive saponin was tested against culex quiquefasciatus. IInd and IV instar larvae of mosquito was exposed to four different concentration of bioactive saponin. 24hrs LC50 and LC90 values were determined using probit analysis method. Obtained result suggests that bioactive compound of *Euphorbia hirta* were more susceptile to IVth instar larvae than II instar larvae [34].

Larvicidal activity

Karthikeyan Agalya priyad arshini *et al*., 2012 synthesised sliver nanoparticles (AgNPs) *Euphorbia hirta* leaf extract concentration range of AgNps (3.125, 6.25, 12.5,25 and 50PPm) and methanol crude extract (50,100,150, 200 and 250PPm) were tested against malarial vector Anopheles stephensi. The synthesized AgNps exhibited a highest larval mortality against first to fourth instar larvae and pupae. Methanol extract exhibited a lowest larval mortality than the synthesized silver nanoparticles can be potential mosquito larvicidal agents [35].

Sedative and Anxiolytic activity

Lyophilized aqueous extract of *Euphorbia hirta* L. (Euphorbiaceae) has been evaluated for behavioral effects in mice. Sedative properties could be confirmed with high doses (100 mg of dried plant/kg, and more), by a decrease of behavioral parameters measured in non-familiar environment tests, whereas anticonflict effects appeared at lower doses (12.5 and 25 mg of dried plant/kg), by an enhancement of behavioral parameters measured in the staircase test and in the light/dark choice situation test. These findings validate the traditional use of *E. hirta* as a sedative and reveal original anxiolytic properties [36].

Galactogenic activity

The powdered plant, given to female guinea pigs before puberty, increased the development of the mammary glands and induced secretion [37]

Anticancer activity

Cytotoxicity studies of the extracts were performed using the cell line and the non-cytotoxic concentration of the extract was tested for antibacterial activity against the cytopathic dose of the pathogen. These extracts were found to be non-cytotoxic and effective antibacterial agents extracts of

Euphorbia hirta have been found to show selective cytotoxicity against several cancer cell lines. The plant is useful in effective treatment of cancers, particularly malignant melanomas and squamous cell carcinomas [38].

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 [38]

Aflatoxin inhibition activity

An aqueous extract significantly inhibited aflatoxin production on rice, wheat, maize and groundnut [39].

Antihepatoxic activity

The antihepatotoxic effect of *Euphorbia hirta* and Boerhaavia diffusa extracts were evaluated in experimental models of liver injury in rats induced by CCL_4 or paracetamol. Hydroalcoholic extract (HE) from whole plant were tested. The Hepatic dysfunction was accessed by determining different biochemical parameters in serum and tissues. In serum, the activities of enzymes like Aspartate Aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (ALP), alkaline phosphate (ALP), Bilirubin were evaluated. Lipid peroxidation and reduced glutathione were also measured into control and treated rats. *E. hirta* whole plant (HE) showed hepatoprotective activities at doses 125 mg/kg and 250 mg/kg, since serum levels of ALT and AST in rats given the extracts were significantly low ($p<0.05$ and 0.01 respectively) When compare to control CCL_4 or paracetamol-injured rats. Furthered studies were carried on the HE from the whole part of both the plant by using the combination of the extract showed the highest level of antihepatotoxic activity with the hydroalcoholic extract which was effective at doses 75mg/kg and 150 mg/kg, for hepatoprotective activity in CCL4 and paracetamolinjured rats. In experiments comparing the comprising the HE (125-250 and 75- 150 mg/kg) to reference antihepatotoxic substance (silymarin) the HE exhibited a 70 and 80% hepatoprotection compared to the 80 and 90% one exhibited by silymarin in CCL_4 or paracetamol -injured rats respectively. This study demonstrated that hydroalcoholic extract *Euphorbia hirta* and Boerhaavia diffusa was effective in protecting the liver from toxic hepatitis [40].

Conclusions

Euphorbia hirta is a very popular herb amongst practitioners of traditional herbal medicine for its antidiarrhoeal, wound healing, antipyretic, anti-inflammatory, hypoglycemic and sedative activities. Moreover it is also used in different systems of medicine in the treatment of bronchitis, skin diseases, analgesic, gastrointestinal disorders, vomiting, respiratory diseases and pulmonary disorders etc. The aim of the present study investigation was carried out to compile the medicinal properties of different plant parts of *Euphorbia hirta* L. and to compare their traditional uses with scientific evidences.

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