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ROLE OF DIFFERENT PHYTOCONSTITUENTS FROM *EUPHORBIA HIRTA* L. IN DISEASE PREVENTION

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ABSTRACT

Euphorbia hirta L. belongs to the family Euphorbiaceae is widely used as a decoction or infusion to treat various ailments including intestinal parasites, diarrhoea, peptic ulcers, heartburn, vomiting, amoebic dysentery, asthma, bronchitis, hay fever, laryngeal spasms, emphysema, coughs, colds, kidney stones, menstrual problems, sterility and venereal diseases. Phytochemical analysis of *Euphorbia hirta* L. revealed the presence of reducing sugar, alkaloids, flavonoids, sterols, tannins and triterpenoids in the whole plant.

KEYWORDS: *Euphorbia hirta* L., Phytochemical analysis, alkaloids, flavonoids, sterols, tannins and triterpenoids.

INTRODUCTION

Euphorbia is a genus of plants belonging to the family Euphorbiaceae. *Euphorbia hirta* L. is a very popular herb amongst practitioners of traditional herb medicine. It is widely used as a decoction or infusion to treat various ailments including intestinal parasites, diarrhoea, peptic ulcers, heartburn, vomiting, amoebic dysentery, asthma, bronchitis, hay fever, laryngeal spasms, emphysema, coughs, colds, kidney stones, menstrual problems, sterility and venereal

diseases. Moreover, the plant is also used to treat affections of the skin. In this chapter we explore those investigations related to their pharmacological activities.

PHYTOCHMISTRY

Phytochemical analysis of *Euphorbia hirta* L. revealed the presence of reducing sugar, alkaloids, flavonoids, sterols, tannins and triterpenoids in the whole plant. Some of them are well known to possess biological activities (as shown in table 1).

Flavonoids

Epidemiological studies have revealed that polyphenols, including flavonoids, provide a significant protection against development of several chronic diseases such as cardiovascular diseases, cancer, diabetes, infections, aging, and asthma. Two flavonoids have been isolated from *Euphorbia hirta* L. namely quercitrin and myricitrin (Johnson *et al*, 1999; Chen, 1991). In general, flavonoids have been reported to possess several proven medicinal properties including antioxidant (Kandaswami & Middleton, 1994), anti-allergic (Singh *et al*, 2006), anti inflammatory component of asthma (Miller, 2001) and antidiarrheal activity (Galvez et *al*, 1993; Mallavadhani *et al*, 2002). Many of the biological actions of flavonoids have been shown to attribute to their antioxidant properties, either through their reducing capacities or as a result of their possible influence on intracellular redox status (Williams *et al*, 2004). Flavonoids can also interact selectively within the mitogen-activated protein (MAP) kinase signalling pathway, thereby existing antiinflammation (Lee, 2011) and anticancer activity (Ding *et al*, 2010).

Sterols

Different sterols isolated from *Euphorbia hirta* L. which were chemically characterized as cycloarternol, 24- methylene-cycloarternol, sitosterol, euphorbol hexacozonate, 1-hexacosanol, tinyaloxin, campesterol and stigmasterol (Atallah and Nicholas, 1972; Galvez *et al*, 1993; Johnson *et al*, 1999). The compounds 24-methylene-cycloartenol and β-sitosterol have also been found to exert significant and dose-dependent anti-inflammatory effects, when treating acetateinduced ear inflammation (Martinez-Vazquez *et al*, 1999).

Tannins

Tannins are widely known for their anti-inflammatory potential. Euphorbia hirta L. also possesses some of such chemicals. Phytochemicals work synergistically, however, and therefore these tannins may assist in the anti-inflammatory action of the plant. *Euphorbia*

hirta L. presents three hydrolysable tannins, namely, dimeric hydrolysable tannin, euphorbin E and the dimeric dehydroellagitannins, euphorbin A and euphorbin B (Yoshida *et al*, 1990). The following tannins from the leaves of *Euphorbia hirta* L. were also isolated by using physicochemical and spectroscopic methods: gallic acid, 2,4, 6-tri-O-galloyl-D-glucose and 1,2,3,4, 6-penta-O-galloyl- D-glucose as well as the quinic acid ester, 3,4-di-O-galloylquinic acid (Chen 1991).

Triterpenoids

Research has shown that triterpenoids possess anti-inflammatory properties. The triterpenes amyrin, taraxerone (EH-1), taxerol as well as amyrin acetate have been identified from *Euphorbia hirta* L. (Martinez-Vazquez *et al*, 1999; Pinn, 2001; Mukherjee *et al*, 2004). Extracts of the plant were found to contain amyrin, which displayed a significant and dose dependent anti-inflammatory activity against acetate-induced ear inflammation (Martinez-Vazquez *et al*, 1999) or LPS-induced inflammatory model (Shih *et al*, 2010). Two additional triterpenoids, namely, taraxerone and 11α, 12α oxidotaraxerol, have also been found in *Euphorbia hirta* L. These compounds induce both antibacterial and antifungal effects, as tested against fourteen pathogenic bacteria (Abu-Sayeed *et al*, 2005).

Table 1: Chemical compounds isolated from Euphorbia hirta L.

Components	Chemicals	Possible biological Function	References
Flavonoids	Quercitrin; Myricitrin	Antioxidation; Anti-allergy; Antibacterial activity; Molluscicidal activity; anti-diarrheal activi	**Galvez et al, 1993; Kandaswami & Middleton, 1994; Mallavadhani *et al*, 2002; Singh *et al*, 2005; Singh *et al*, 2006; Park & Lee, 2006; Sudhakar *et al*, 2006; Rajeh *et al*, 2010; Ding *et al*, 2010; Lee, 2011**
Sterols	Cycloarternol; 24methylene-cycloarternol; β-sitosterol; euphorbol hexacozonate; 1-hexacosanol; tinyaloxin; campesterol; stigmasterol	anti-inflammatory effects	**Martinez-Vazquez *et al*, 1999**

Tannin	euphorbin E; euphorbin A; euphorbin B; gallic acid; 2,4, 6-tri-O-galloyl-D-glucose; 1,2,3,4, 6-penta-O-galloyl-β-D-glucose; 3,4-di-Ogalloylquinic acid	anti-inflammatory activity	**Yoshida *et al*, 1990; Chen 1991**
Triterpenoids	α-amyrin; β-amyrin; taraxerone; taxerol; β-amyrin acetate; taraxerone; 11α, 12α-oxidotaraxerol	anti-inflammatory activity; anti-pruritic activity; antidiabetic activity; antimicrobial activity	**Martinez-Vazquez *et al*, 1999; Pinn, 2001; Mukherjee *et al*, 2004; Abu-Sayeed *et al*, 2005; Park & Lee, 2006; Shih *et al*, 2010**

Pharmacology

Effects on GI system

Protective effect of *Euphorbia hirta* L. against antitubercular drug-induced cytotoxicity was observed in freshly isolated hepatocytes. Antitubercular drug intoxication alters liver function by affecting aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, triacylglycerol, cholesterol, total protein, albumin, total and direct bilirubin. A dose-dependent increase in percent viability was obtained when antitubercular drug exposed HepG2 cells were treated with different concentrations of alcoholic extract of *Euphorbia hirta* L. (125, 250, 500 and 1000 mg/mL). The effectiveness of liver protection was comparable to a standard hepatoprotective drug silymarin (Brindha *et al*, 2010). The antihepatotoxic effect of *Euphorbia hirta* L. extracts were also evaluated in experimental models of liver injury in rats induced by CCL4 or paracetamol (Tiwari *et al*, 2011). Carbon tetrachloride and paracetamol are known to cause liver damage (Recknagel, 1983; James *et al.*, 2003). When administered to rats, they act by inducing oxidative damages to liver cells which leads to cellular necrosis. *Euphorbia hirta* L. exhibited a 70 and 80% hepatoprotection compared to the 80 and 90% one exhibited by silymarin in CCL4 or paracetamol-injured rats, respectively. The extract *Euphorbia hirta* L. was demonstrated effectively in protecting the liver from toxic hepatitis.

Aqueous leaf extract of *Euphorbia hirta* L. was shown to decrease the gastrointestinal motility in normal rats and decreased the effect of castor oil-induced diarrhoea in mice (Hore *et al*, 2006; Galvez *et al*, 1993). The anti-diarrheal activity of *Euphorbia hirta* L. was also effective in arachidonic acid- and prostaglandin E-2 induced diarrhoea (Galvez *et al*, 1993).

Quercetin-3-O-D-rhamnoside, a flavonoid, was found to be the active component with anti-diarrheal activity (Galvez *et al*, 1993; Mallavadhani *et al*, 2002).

Analgesic, antipyretic and anti-inflammatory actions

Euphorbia hirta L. exists a dose-dependent analgesic action against chemical (writhing test) and thermic (hot plate test) stimuli at the doses of 20 and 25 mg/kg which is inhibited by pretreatment of naloxone, a specific morphinic antagonist compound. Therefore, it exerts central analgesic properties.

In addition, *Euphorbia hirta* L. was effectively against acute pain in carrageenan-induced edema model (Lanhers *et al*, 1991). An antipyretic activity was obtained at the sedative doses of 100 and 400 mg/kg, on the yeast-induced hyperthermia (Lanhers *et al*, 1991). Anti inflammatory effects of *Euphorbia hirta* L. were shown in 12-o-tetradecanoyl phorbol acetate induced ear edema (Martinez-Vazquez *et al*, 1999; Lanhers *et al*, 1991). Although *Euphorbia hirta L.* was ineffective in Freund's adjuvant-induced rheumatoid arthritis model, it reduced the inflammatory hyperalgia of rheumatoid arthritis (Lanhers *et al*, 1991). The molecular pharmacology basis of this anti-inflammatory effect is revealed in an established inflammation model in lipopolysaccharide (LPS)-activated macrophages (fig 1). In the concentration range without showing cytotoxicity, *Euphorbia hirta* L. produced a remarkable anti-inflammatory effect via its active component of beta-amyrin and showed a dose-related inhibition against LPS-induced NO production (Camuesco *et al*, 2004; Comalada *et al*, 2005; Shih *et al*, 2010). The extract of *Euphorbia hirta* L. and beta-amyrin are able to block most of the iNOS protein functions and NO induction (fig 2). The extract of *Euphorbia hirta* L. and beta-amyrin were not as potent as Indomethacin in preventing LPS-induced PGE2 production (Shih et al, 2010). This indicated that the extract of *Euphorbia hirta* L. and its active component, beta-amyrin, may have less gastrointestinal adverse effect than indomethacin does. The extract of *Euphorbia hirta* L. and its component beta-amyrin could therefore be new selective NO inhibitors with great potential in treating endotoxin-induced inflammation.

In asthma & Inhibition of allergic reactions

Euphorbia hirta L. has been used to treated asthma as a folk medicine (Watanabe *et al*, 2005). *Euphorbia hirta* L. functions for the treatment of asthma is probably through synergistic anti-inflammatory and antioxidant activities of especially the flavonoids, sterols and triterpenoids (Park & Lee, 2006). Asthma has long been associated with chronic inflammation and an overall increase in reactive groups and oxidative stress (Nadeem *et al*,

2003). *Euphorbia hirta* L. also existed significant activity to prevent early and late phase allergic reactions and thereby asthma. *Euphorbia hirta* L. reduced asthma attack has been shown as effective as corticosteroid in the BALB/c asthmatic mouse mode (Ekpo & Pretorius, 2008). The possible active component of *Euphorbia hirta* L. is thought to be Quercitrin. *Euphorbia hirta* L. ethanol extract significantly prevented eosinophil accumulation and eosinophil peroxidase activity and reduced the protein content in bronchoalveolar lavage fluid in a 'mild' model of asthma (Singh *et al*, 2006).

Taken together, *Euphorbia hirta* L. is a very potent herb medicine in treatment of asthma. Ethanol extract of *Euphorbia hirta* L. has also been shown to inhibit polysorbate 80-induced degranulation of isolated peritoneal mast cells in vitro. Thus anti-inflammatory activity of *Euphorbia hirta* L. could be attributed to mast cell membrane stabilization, thereby inhibiting the release of inflammatory mediators (Ramesh & Padmavathi, 2010). *Euphorbia hirta* L. ethanol extracts also significantly inhibited dextran-induced rat paw edema, attenuated the release of interleukin-4 (IL-4) and augmented IFN-gamma in ovalbumin-sensitized mouse splenocytes (Singh *et al*, 2006). Anaphylactic allergic reaction is a life-threatening syndrome induced by the sudden systemic release of inflammatory mediators such as histamine and pro-inflammatory cytokines and can be elicited by various stimulators including compound 48/80 (N-methyl-p-methoxy-phenethylamine) and anti-IgE (Paul *et al*, 1993). Compound 48/80-induced mortality could also be reduced by *Euphorbia hirta* L. ethanol extract administration in Wistar rats (Youssouf *et al*, 2007).

Burn wound healing Actions

Tissue damage from excessive heat, electricity, radioactivity or corrosive chemicals that destroy (denature) protein in the exposed cells is called a burn. Burns disrupt haemostasis because they destroy the protection afforded by the skin. They permit microbial invasion and infection, loss of body fluid and loss of thermoregulation. Various extracts of *Euphorbia hirta* L. exhibited antimicrobial activity against various microbes including those causing burn and wound infections like Pseudomonas aeruginosa and Staphylococcus aureus (Sudhakar *et al*, 2006; Rajeh *et al*, 2010). Hence, *Euphorbia hirta* L. could be beneficial in the management of burn wounds. The ethanol extract of whole plant of *Euphorbia hirta* L. was screened for burn wound healing activity in rats as 2% W/W cream. The study was carried out based on the assessment of percentage reduction in original wound. *Euphorbia hirta* L. was showed significant burn wound healing activity (Jaiprakash *et al*, 2006).

Antioxidative Action

Free radicals have been claimed to play an important role in affecting human health by causing several chronic diseases, such as cancer, diabetes, aging, atherosclerosis, hypertension, heart attack and other degenerative diseases (Raghuveer *et al*, 2009). These free radicals are generated during body metabolism. Exogenous intake of antioxidants can help the body scavenge free radicals effectively. There is a noticeable interest in antioxidants, especially in those which can prevent the presumed deleterious effects of free radicals in the human body, and to prevent the deterioration of fats and other constituents of foodstuffs. In both cases, there is a preference for antioxidants from natural rather than from synthetic sources (Molyneux *et al*, 2004). At present, most of the antioxidants are manufactured synthetically. The main disadvantage with the synthetic antioxidants is the in vivo side effects (Ramamoorthy *et al*, 2007). Previous studies reported that butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) accumulate in the body and result in liver damage and carcinogenesis (Jiangning *et al,* 2005). Phytochemical screening of *Euphorbia hirta* L. revealed the presence of several chemicals, including flavanoids, which may be responsible for its strong anti-oxidative activity (Basma *et al,* 2011). The anti-oxidant activity of *Euphorbia hirta* L. was comparable with that of ascorbic acid and found to be dose dependent (Basma *et al,* 2011).

Antidiabetic and free radicals scavenging potential

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is well documented that chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and eventually the failure of organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Daily treatment of ethanol and petroleum ether flower extracts of *Euphorbia hirta* L. for three weeks significantly reduced alloxan-induced hyperglycemia, triglycerides and cholesterol (Kumar *et al*, 2010). Other biochemical parameters such as serum creatinine, urea and alkaline phosphatase levels were also found to be decreased whereas total proteins were found to be increased after treatments. Both extracts of *Euphorbia hirta* L. have significant antioxidant activity compared to other well characterized, standard antioxidant systems. Free radical scavenging potential was assessed against DPPH. The reductive capabilities of extract were compared with ascorbic acid and BHA. The extract showed dose dependent reducing power. This additional antioxidative effect of *Euphorbia hirta* L. may provide extract benefit in preventing oxidative-induced complications in diabetic patients.

Anti-infective Action

The antimicrobial activities of the methanol 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 (Sudhakar *et al*, 2006; Rajeh *et al*, 2010; Singh *et al*, 2011). 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*, followed by *S. aureus* and *P. mirabilis.* 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. Therefore, methanol extract of *Euphorbia hirta* L. possessed a broad spectrum of antimicrobial activity against studied bacterial strains. However, its inhibitory effect on H. pylori effects was weak (Ndip *et al*, 2007). Interestingly, *Euphorbia hirta* L. was not found to be very effective for anti-fungal activity by others (Abu-Sayeed *et al*, 2005; Singh *et al*, 2011). Taken together, *Euphorbia hirta L*. can be used to discover new bioactive natural products that may serve as leads in the development of new pharmaceuticals. The antiretroviral activities of extracts of *Euphorbia hirta* L. were investigated in vitro on the MT4 human T lymphocyte cell line. A dose-dependent inhibition activity was observed for HIV- 1, HIV-2 and SIV (mac251) all three viruses. Methanol extract was found to exert a higher antiretroviral effect than that of the aqueous extract (Gyuris *et al*, 2009).

Molluscicidal activity and Larvicidal activities

Mosquito-transmitted diseases remain a major cause of the loss of human life worldwide with more than 700 million people suffering from these diseases annually (Taubes 1997). Mosquito-borne diseases have an economic impact, including loss in commercial and labor

outputs, particularly in countries with tropical and subtropical climates; however, no part of the world is free from vector-borne diseases (Fradin and Day 2002). Larvicidal activity of *Euphorbia hirta* L. has been found in petroleum ether extract with LC50 value 272.36 ppm (Abdul Rahuman *et al*, 2008). Many aquatic snails act as vectors for the larvae of trematodes and thereby, cause a number of diseases (Bali *et al.*, 1986). Two diseases carried by aquatic snails, schistosomiasis and fascioliasis, cause immense harm to man and his domestic animals. The freshwater vector snail *Lymnaea acuminata* is the intermediate hosts of Fasciola hepatica and Fasciola gigantic (Hyman, 1970). Which caused endemic fascioliasis in sheep, cattle, goat and others herbivorous animal. Aqueous stem bark and leaf extracts of plant *Euphorbia hirta* L. have potent molluscicidal activity. Sub-lethal doses (40% and 80% of LC50) of aqueous stem bark and leaf extracts of this plant also significantly alter the levels of total protein, total free amino acid, nucleic acids (DNA and RNA) and the activity of enzyme protease and acid and alkaline phosphatase in various tissues of the vector snail *Lymnaea acuminata* in time and dose dependent manners (Singh *et al*, 2005).

As Immunostimulant effect in aquaculture

Euphorbia hirta L. 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 (FAO, 2009; Mohanty & Sahoo, 2010). 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 (Logambal *et al.*, 2000; Dügenci *et al*., 2003; Rairakhwada *et al.*, 2007). *Pseudomonas fluorescens* Flugge (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 (Saharia & Prasad, 2001). The leaf extracts of *Euphorbia hirta* L. administered through the diet enhanced the nonspecific defence 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 (Pratheepa and Sukumaran, 2011). Immunostimulatory activity of *Euphorbia hirta* L. was

also found to enhance in vitro phagocytosis of neutrophils and macrophages (Ramesh and Padmavathi, 2010).

Anti-anxiety Action

Stress is increasingly recognized as the precipitant of several psychiatric illnesses including anxiety and depression (McEwen, 2000). When rats subjected to chronic immobilization stress (CIS) or forced swim stress (FSS) showed anxiety in the elevated plus maze (EPM) and the open field test (OFT) (Anuradha *et al*., 2008; Govindarajan *et al*., 2006; Vyas *et al*., 2002). In addition to anxiety, stress is also known to produce learning and memory deficits. For example, chronic stress impaired learning in the T-maze and radial arm maze (Ramkumar *et al*., 2008; Srikumar *et al*., 2006, 2007) or in other paradigms such as the Barnes maze and Morris water maze (Bodnoff *et al*., 1995; McLay *et al*., 1998). The dopaminergic and cholinergic neurotransmitter systems have been shown to be involved in mediating the stress induced deficits (Srikumar *et al.*, 2006, 2007). CIS increased the acetylcholinesterase (AChE) activity in the frontal cortex, hippocampus, and septum, while *Euphorbia hirta* L. treatment brought it to normal levels. FSS increased the AChE activity only in the septum, and *Euphorbia hirta* L. treatment marginally normalized this change. Chronic stress not only induces impairment of learning and memory but also precipitates several affective disorders including depression and anxiety. Sedative properties of aqueous extract of *Euphorbia hirta* L. have been confirmed at high dose (100 mg of dried plant/kg) by showing a decrease of behavioral parameters measured in non-familiar environment tests (activitest and staircase test). For anti-conflict effects appeared at lower doses (12.5 and 25 mg of dried plant/kg) by revealing an enhancement of behavioral parameters measured in the staircase test and in the light/dark choice situation test (Lanhers *et al,* 1990). Anxiolytic property of *Euphorbia hirta* L. was also demonstrated in chronically stressed rats subjected to EPM and OFT (Anuradha *et al,* 2008). *Euphorbia hirta* L. treatment showed marked anti-anxiety activity in CIS rats. Co-treatment of rats with flumazenil, bicuculline or picrotoxin resulted in a significant reduction of anxiolytic effect of *Euphorbia hirta* L. indicating that its actions are mediated through GABA-A receptor-benzodiazepine receptor-Cl channel complex. Acetylcholine and the cholinergic system are also known to involve in anxiety. Further study showed that anxiolytic effects of *Euphorbia hirta* L. in rats subjected to CIS was due to suppression of CIS-induced AChE activity in the frontal cortex, hippocampus, and septum brain regions (Anuradha *et al,* 2010). Together with GABAmimic effect and AChE reducing effect may explain the anxiolytic activity of *Euphorbia hirta* L.

Effect on renal system

Dickshit (1934) first reported the presence of a toxic principle in *Euphorbia hirta* L. 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 (Hazleton and Hellerman, 1954). *Euphorbia hirta* L. is locally used to treat numerous diseases, including hypertension and edema in Africa (Khan *et al*., 1980). Diuretic effect of the *E. hirta* L. 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* L. 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 (Johnson *et al*, 1999).

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 (Opie, 1992). *Euphorbia hirta* L. 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 *Euphorbia hirta* L. (10 mg/100 mg body weight) also possessed anti-dipsogenic activities (Williams *et al*, 1997). Both diuresis and ACE inhibition effects of *Euphorbia hirta* L. may explain its antihypertensive effects.

CONCLUSION

Although *Euphorbia hirta* L. has been widely used to treat various diseases in many countries, most of molecular mechanisms have not been fully explored. However, the pharmacological mechanisms of *Euphorbia hirta* L. in asthma attacks and hypertension were relatively clear. The former can be due to its potent anti-inflammatory and anti-oxidative activities. The later may work through its actions of diuretic activity and ACE inhibition. For anxiolytic effects of *E. hirta* L. is thought to be mediated through GABA-A mediated Cl channel as well as AChE reduction. The anti-infection of *Euphorbia hirta* L. is due to its

direct bactericidal activity. Anti inflammatory and antioxidative activities of *Euphorbia hirta* L. can also be expected to use in treating scald, preventing sepsis or other chronic inflammatory diseases. In overall, there are still many clinical applications of *E. hirta* L. remained to be investigated for their molecular mechanisms.

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REFERENCES

1. Abdul Rahuman, A., Geetha Gopalakrishnan, Venkatesan, P. and Kannappan, Geetha (2008). Larvicidal activity of some Euphorbiaceae plant extracts against *Aedes aegypti* and *Culex quinquefasciatus* (Diptera: Culicidae). Parasitolog Research; 102(5): 867–873.
2. Abu-Sayeed, M., Ali, M.A., Bhattacharjee, P.K., Islam, A., Astaq, G.R.M., Khan, M. and Yeasmin, S. (2005). Biological evaluation of extracts and triterpenoids of *Euphorbia hirta*. Pakistan Journal of Science and Industrial Research; 48(2): 122–125.
3. Atallah A.M., and Nicholas H.J. (1972). Triterpenoids and steroids of *Euphorbia pilulifera*. Phytochemistry; 2: 1860–1868.
4. Anuradha, H., Srikumar, B.N., Shankaranarayana Rao, B.S. (2008). *Euphorbia hirta* reverses chronic stress-induced anxiety and mediates its action through the GABAA receptor benzodiazepine receptor-Cl2 channel complex. Journal of Neural Transmission; 115(1): 35–42.
5. Anuradha, H., Srikumar, B.N., Deepti, N., Shankaranarayana Rao, B.S., and Lakshmana, M. (2010). Restoration of acetylcholinesterase activity by *Euphorbia hirta* in discrete brain regions of chronically stressed rats. Pharmaceutical Biology; 48(5): 499-503.
6. Bali, H.S., Singh, S. & Sharma, S. (1986). The distribution and ecology of vectors snails of Punjab. Indian Journal of Ecology; 13: 31–37.
7. Basma, A.A., Zakaria, Z., Latha, L.Y. and Sasidharan, S. (2011). Antioxidant activity and phytochemical screening of the methanol extracts of *Euphorbia hirta* L. Asian Pacific Journal of Tropical Medicine; 4(5): 45-52.
8. Bodnoff, S.R., Humphreys, A.G., Lehman, J.C., Diamond, D.M., Rose, G.M. & Meaney, M.J. (1995) Enduring effects of chronic corticosterone treatment on spatial learning,

synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. The Journal of Neuroscience; 15(1): 61–69.

9. Brindha, D., Saroja, S., Jeyanthi, G.P. (2010) Protective potential correction of potential of *Euphorbia hirta* against cytotoxicity induced in hepatocytes and a HepG2 cell line. Journal of Basic and Clinical Physiology and Pharmacology; 21(4): 401-413.
10. Camuesco, D., Comalada, M., Rodriguez-Cabezas, M.E., Nieto, A., Lorente, M.D., Concha, A., Zarzuelo, A. and Galvez J. (2004) The intestinal anti-inflammatory effect of quercitrin is associated with an inhibition in iNOS expression. British Journal of Pharmacology; 143(7): 908–918.
11. Chen, L. (1991). Polyphenols from leaves of *Euphorbia hirta* L. Zhongguo Zhong Yao Za Zhi; 16(1): 38–39, 64.
12. Comalada, M., Camuesco, D., Sierra, S., Ballester, I., Xaus, J., Galvez, J. & Zarzuelo, A. (2005). In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-kappa B pathway. The European Journal of Immunology; 35(2): 584–592.
13. Dickshit, R.A.O. (1934). Effect of Euphorbia hiffa on the cardiovascular system. Proceedings of Indian Science Congress; p. 349.
14. Ding, M., Zhao, J., Bowman, L., Lu, Y. and Shi, X. (2010). Inhibition of AP-1 and MAPK signaling and activation of Nrf2/ARE pathway by quercitrin. International journal of oncology; 36(1): 59-67.
15. Dügenci, S.K., Arda, N. and Candan, A. (2003). Some medicinal plants as immunostimulant for fish. Journal of Ethnopharmacology; 88(1): 99–106.
16. Ekpo, O.E. and Pretorius, E. (2008). Using The BALB/c Asthmatic Mouse Model to Investigate the Effects of Hydrocortisone and a Herbal Asthma Medicine on Animal Weight. Scandinavian Journal of Laboratory Animal Science; 35(4): 265-280.
17. Fradin,, M.S. and Day, J.F. (2002). Comparative efficacy of insect repellents against mosquitoes bites. The New England journal of medicine; 347: 13–18.
18. Galvez, J., Zarzuelo, A., Crespo, M.E., Lorente, M.D., Ocete, M.A. and Jiménez, J. (1993). Antidiarrhoeic activity of *Euphorbia hirta* extract and isolation of an active flavonoid onstituent. Planta Medica; 59(4): 333-336.
19. Govindarajan, A., Shankaranarayana Rao, B.S., Nair, D., Trinh, M., Mawjee, N., Tonegawa, S. and Chattarji, S. (2006). Transgenic brainderived neurotrophic factor expression causes both anxiogenic and antidepressant effects. Proceedings of the National Academy of Sciences USA; 103(35): 13208–13213.

20. Gyuris, A., Szlávik, L., Minárovits, J., Vasas, A., Molnár, J. and Hohmann, J. (2009). Antiviral activities of extracts of *Euphorbia hirta* L. against HIV-1, HIV-2 and SIVmac251. In Vivo; 23(3): 429-432.
21. Hazleton, L.W., and Hellerman, R.C., (1954). Studies on the pharmacology of *E. piluliera*. Journal of American Pharmaceutical Association; 40: 474–476.
22. Hore, S.K., Ahuja, V., Mehta, G., Pardeep Kumar, Pandey, S.K. & Ahmad, A.H. (2006). Effect of aqueous *Euphorbia hirta* leaf extract on gastrointestinal motility. Fitoterapia: 77: 35– 38.
23. Hyman, L.H. (1970). The invertebrate; VI. Mollusca I. Mc Graw Hill, New York.
24. Jaiprakash B, Chandramohan, Reddy DN. (2006). Burn wound healing activity of *Euphorbia hirta*. Ancient Science of Life; 15(3&4): 01-03, ISSN: 0257-7941
25. Jiangning, G., Xinchu, W., Hou, W., Qinghua, L. & Kaishun, B. (2005). Antioxidants from a Chinese medicinal herb - *Psoralea corylifolia* L. Food Chemistry; 91(2): 287-292.
26. James, LP., Mayeux, P.R. and Hinston, J.A. (2003). Acetaminophen-induced hepatotoxicity. Drug Metabolism and Disposition; 31: 1499-1506.
27. Johnson, P.B., Abdurahman, E.M., Tiam, E.A., Abdu-Aguye, I. and Hussaini, I.M. (1999) *Euphorbia hirta* leaf extracts increase urine output and electrolytes in rats. Journal of Ethnopharmacology; 65: 63–69.
28. Kandaswami, C. and Middleton, E. (1994). Free radical scavaging and antioxidant activity of plant flavonoids. Advances in Experimental Medicine and Biology; 366: 351– 376.
29. Khan, M.R., Ndaolio, G., Nkunya, M.H.H., Wevers, H. and Sawhney, A. (1980). Studies on African medicinal plants. Part I. Preliminary screening of medicinal plants for antibacterial activity. Planta Medica; Suppl:91–97.
30. Kobuchi, H., Roy, S., Sen, C.K., Nguyen, H.G. and Packer, L. (1999). Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway. American Journal of Physiology; 277(3): 403–411.
31. Kong, A.N., Yu, R., Chen, C., Mandlekar, S. and Primiano, T. (2000). Signal transduction events elicited by natural products: role of MAPK and caspase pathways in homeostatic response and induction of apoptosis. Archives of pharmacal research; 23(1): 1–16.
32. Kumar, S., Malhotra, R. and Kumar, D. (2010). Antidiabetic and free radicals scavenging potential of *Euphorbia hirta* flower extract. Indian journal of Pharmaceutical Sciences; 72(4): 533-537.

33. Lanhers, M.C., Fleurentin, J., Cabalion, P., Rolland, A., Dorfman, P., Misslin, R. and Pelt, J.M. (1990). Behavioral effects of *Euphorbia hirta* L. sedative and anxiolytic properties. Journal Ethnopharmacology; 29(2): 189-198.
34. Lanhers, M.C., Fleurentin, J., Dorfman, P., Mortier, F. and Pelt, J.M. (1991) Analgesic, antipyretic and anti-inflammatory properties of *Euphorbia hirta*. Planta Medica; 57(3): 225-231.
35. Lee, J.K. (2011) Anti-inflammatory effects of eriodictyol in lipopolysaccharide-stimulated raw 264.7 murine macrophages. Archives Pharmacal Research; 34(4): 671-679.
36. Logambal, S.M., Venkatalakshmi, S. and Dinakaran, M.R. (2000). Immunostimulatory effect of leaf extract of *Ocimum sanctum* Linn. In *Oreochromis mossambicus* (Peters). Hydrobiologia; 430: 113–120.
37. Mallavadhani, U.V., Gayatri Sahu, Narasimhan, K., Muralidhar, J. (2002). Quantitative Estimation of an Antidiarrhoeic Marker in *Euphorbia hirta* Samples. Pharmaceutical Biology; 40(2): 103-106.
38. Martinez-Vazquez, M., Ramirez Apan, T.O., Lazcano, M.E. & Bye, R. (1999). Antiinflammatory active components from n-Hexane extract of *Euphorbia hirta*. The Revista de la Sociedad Química de México; 43: 103-105.
39. McEwen, B.S. (2000). The neurobiology of stress: From serendipity to clinical relevance. Brain Research; 886(1-2): 172–189.
40. McLay, R.N., Freeman, S.M. and Zadina, J.E. (1998). Chronic corticosterone impairs memory performance in the Barnes maze. Physiology & Behavior; 63: 933–937.
41. Miller, A.L. (2001). The etiologies, patho-physiology and alternative complementary treatment of asthma. Alternative medicine review; 6(1): 20–47.
42. Mohanty, B.R. and Sahoo, P.K. (2010) Immune responses and expression profiles of some immune-related genes in Indian major carp, *Labeo rohita* to Edwardsiella tarda infection. Fish and Shellfish Immunology; 28: 613–621.
43. Molyneux, P. (2004). The use of the stable free radical diphenylpicrylhydrazyl (DPPH) for estimating antioxidant activity. Songklanakarin Journal of Science and Technology; 26(2): 211-219.
44. Mukherjee, K.S., Mukhopadhyay, B., Mondal, S., Gorai, D. and Brahmachari, G. (2004). Triterpenoid Constituents of *Borreria articularis*. Journal of the Chinese Chemical Society; 51(1): 229-231

45. Nadeem, A., Chhabra, S.K., Masood, A. and Raj, H.G. (2003). Increased oxidative stress and altered levels of antioxidants in asthma. The Journal of Allergy and Clinical Immunology; 111(1): 72-78.
46. Ndip, R.N., Tarkang, A.E.M., Mbullah, S.M., Luma, H.N., Malongue, A., Ndip, L.M., Nyongbela, K., Wirmumd, C. and Efange, S.M.N. (2007). In vitro anti-Helicobacter pylori activity of extracts of selected medicinal plants from North West Cameroon. Journal of Ethnopharmacology; 114(3): 452–457.
47. Opie, L. H. (1992). Angiotensin Converting Enzyme Inhibitors: Scientific Basis for Clinical Use, p. 259.
48. Park, S.J. and Lee, Y.C. (2006). Antioxidants as Novel Agents for Asthma. Mini Reviews in Medicinal Chemistry; 6(2): 235-240.
49. Paul, W.E., Seder, R.A. and Plaut, M. (1993). Lymphokine and cytokine production by Fc epsilon RI+ cells. Advances in Immunology; 53: 1.
50. Pinn, G. (2001). Herbal therapy in respiratory diseases. Australian Family Physician; 30(8): 775–779.
51. Pratheepa, V. and Sukumaran, N. (2011). Specific and nonspecific immunostimulation study of *Euphorbia hirta* on Pseudomonas fluorescens-infected *Cyprinus carpio* Pharmaceutical Biology; 49(5): 484–491.
52. Raghuveer, C. and Tandon, R.V. (2009). Consumption of functional food and our health concerns. Pakistan Journal of Physiology; 5(1): 76-83.
53. Rairakhwada D, Pal AK, Bhathena ZP, Sahu NP, Jha A, Mukherjee SC. (2007). Dietary microbial levan enhances cellular non-specific immunity and survival of common carp (*Cyprinus carpio*) juveniles. Fish and Shellfish Immunology; 22(4): 477–486.
54. Rajeh, M.A., Zuraini, Z., Sasidharan, S., Latha, L.Y. and Amutha, S. (2010). Assessment of *Euphorbia hirta* L. leaf, flower, stem and root extracts for their antibacterial and antifungal activity and brine shrimp lethality. Molecules; 15(9): 6008-6018.
55. Ramamoorthy, P.K. and Bono, A. (2007). Antioxidant activity, total phenolic and flavonoid content of *Morinda citrifolia* fruit extracts from various extraction processes. Journal of Engineering Scuences and Technology; 2: 70-80.
56. Ramkumar, K., Srikumar, B.N., Shankaranarayana Rao, B.S. and Raju, T.R. (2008). Selfstimulation rewarding experience restores stress induced CA3 dendritic atrophy, spatial memory deficits and alterations in the levels of neurotransmitters in the hippocampus. Neurochemical Research; 33(9): 1651– 1662.

57. Ramesh, K.V. and Padmavathi, K. (2010). Assessment of immunomodulatory activity of *Euphorbia hirta* L. Indian Journal of Pharmaceutical Sciences; 72(5): 621-625.
58. Recknagel, R.O. (1983). A new direction in the study of carbon tetrachloride hepatotoxicity. Life Sciences. 33: 401-408.
59. Saharia, P.K. and Prasad, K.P. (2001). Development of co-agglutination kit for the diagnosis of *Pseudomonas fluorescence* infection in fishes. Asian Fisheries Sciences; 14: 293–300.
60. Shih, M.F., Cheng, Y.D., Shen, C.R. and Cherng, J.Y. (2010). A molecular pharmacology study into the anti-inflammatory actions of *Euphorbia hirta* L. on the LPS-induced RAW 264.7 cells through selective iNOS protein inhibition. Journal of Natural Medicines; 64(3): 330-335.
61. Singh, B., Dutt, N., Kumar, D., Singh, S. and Mahajan, R. (2011). Taxonomy, Ethnobotany and Antimicrobial Activity of *Croton bonplandianum*, *Euphorbia hirta* and *Phyllanthus fraternus.* Journal of Advances in Developmental Research; 2(1): 21-29.
62. Singh, G.D., Kaiser, P., Youssouf, M.S., Singh, S., Khajuria, A., Koul, A., Bani, S., Kapahi, B.K., Satti, N.K., Suri, K.A. and Johri, R.K. (2006). Inhibition of Early and Late Phase Allergic Reactions by *Euphorbia hirta* L. Phytotherapy Research; 20(4): 316–321.
63. Singh, S.K., Yadav, R.P., Tiwari, S. and Singh, A. (2005). Toxic effect of stem bark and leaf of *Euphorbia hirta* plant against freshwater vector snail *Lymnaea acuminata*. Chemosphere; 59(11): 263–270.
64. Spencer, J.P.E., Kuhnle, G.G.C., Williams, R.J. and Rice-Evans, C. (2003). Intracellular metabolism and bioactivity of quercetin and its in vivo metabolites. Biochemical Journal; 372: 173–181.
65. Srikumar, B.N., Raju, T.R. and Shankaranarayana Rao, B.S. (2006). The involvement of cholinergic and noradrenergic systems in behavioral recovery following oxotremorine treatment to chronically stressed rats. Neuroscience; 143(3): 679–688.
66. Srikumar, B.N., Raju, T.R. and Shankaranarayana Rao, B.S. (2007). Contrasting effects of bromocriptine on learning of a partially baited radial arm maze task in the presence and absence of restraint stress. Psychopharmacology; 193(3): 363–374.
67. Sudhakar, M., Rao, Ch.V., Rao, P.M., Raju, D.B. and Venkateswarlu, Y. (2006). Antimicrobial activity of *Caesalpinia pulcherrima*, *Euphorbia hirta* and *Asystasia gangeticum*. Fitoterapia; 77(5): 378–380.
68. Sun, H., Fang, W-S., Wang, W-Z., and Hu, Chun. (2006). Structure-activity relationships of oleanane- and ursanetype triterpenoids. Botanical Studies; 47: 339-368.

69. Taubes, G. (1997). A mosquito bites back. New York Times Magazine 24 August; 40–46.
70. Tiwari1, P., Kumar, K. Ashish Kumar Pandey, A.K., Pandey, A. and Sahu, P.K. (2011). Antihepatotoxic Activity of Euphorbia hirta and by using the combination of *Euphorbia hirta* and *Boerhaavia diffusa* extracts on Some Experimental Models of Liver Injury in Rats. International Journal of Innovative Pharmaceutical Research. 2(2): 126-130.
71. VanWyk, B-E., Van Oudtshoorn, B. and Gericke, N. (2000). Medicinal Plants of South Africa, 2nd edn. Briza, Pretoria.
72. Vyas, A., Mitra, R., Shankaranarayana Rao, B.S. and Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. The Journal of Neuroscience; 22: 6810–6818.
73. Watanabe, T., Rajbhandari, K.R., Malla, K.J. and Yahara, S. (2005). A handbook of medicinal plants of Nepal Ayur Seed Life Environmental Institute, Japan, 262.
74. Williams, R.J., Spencer, J.P.E. and Rice-Evans, C. (2004). Flavonoids: antioxidants or signaling molecules. Free Radical Biology & Medicine; 36(7): 838–849.
75. Williams, L.A.D., Gossell-Williams, M., Sajabi, A., Barton, E.N. and Fleischhacker, R. (1997). Angiotensin Converting Enzyme Inhibiting and Anti-dipsogenic Activities of *Euphorbia hirta* Extracts. Phytotherapy Research, 11: 401–402.
76. Yoshida, T., Namba, O., Chen, L. and Okuda, T. (1990). Euphorbin E: A Hydrolysable tannin dimer of highly oxidized structure from *Euphorbia hirta*. Chemical & Pharmaceutical Bulletin (Tokyo); 38: 1113–1115.
77. S.E. & Johri, R.K. (2007). Anti-anaphylactic effect of *Euphorbia hirta*. Fitoterapia; 78(7-8): 535–539.