

Review

Euphorbia hirta (Feiyangcao): A review on its ethnopharmacology, phytochemistry and pharmacology

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Accepted 15 March, 2012

A bibliographic investigation was carried out by gathering and analyzing the recognized books, including Chinese herbal classic, the Internet (Google Scholar, Baidu Scholar), and scientific databases (Pubmed, Scifinder, Scopus, CNKI, ACS, and Web of Science) for available information on *Euphorbia hirta*. Whole plants of *E. hirta* have been used in traditional Chinese medicine (TCM) due to its properties that can cure and detoxify fever, promote diuresis, stop itching, and induce prolactin. Traditional uses of *E. hirta* are also recorded in some other pan-tropical areas, where it has been used for over 10 types of diseases. A number of chemical constituents, including flavonoids, terpenoids and phenols, have been isolated and identified from *E. hirta*. Various biological evaluations have been reported for its importance. Modern pharmacological investigation demonstrated that its crude extracts and active compounds possesses wide pharmacological effects, such as antibacterial, anti-inflammatory, antioxidant, sedative and anti-allergy. The current study summarizes the updated information concerning the ethnopharmacology, phytochemistry, and pharmacology of *E. hirta* as well as its toxicology, and discusses the existing problem and future research direction of *E. hirta*.

Key words: *Euphorbia hirta*, traditional Chinese medicines, ethnopharmacology, phytochemistry, pharmacology.

INTRODUCTION

Euphorbia hirta, an important medicinal herb, belongs to genus *Euphorbia*, family Euphorbiaceae. As a widely used local and traditional Chinese medicine (TCM) in clinical practice, the whole plant is commonly applied to cure various diseases, especially gastrointestinal disorders (including intestinal parasites, diarrhea, peptic ulcers, heartburn, vomiting, and amoebic dysentery), affections of the skin and mucous membranes (including warts, scabies, tinea, thrush, aphthae, fungal affections, and measles), and respiratory system disorders (including asthma, bronchitis, hay fever, laryngeal spasms, emphysema, coughs, and colds) (Zhong yao da ci dian, 1986; Zhong hua ben cao, 1999). *E. hirta* is native to Central America. It was introduced into Southeast Asia a long time ago and has since spread throughout. It is a

very common herb in the pan-tropic and partly subtropic areas worldwide, including China, India, Philippines, Australia, Africa, Malaysia, and so on. In China, *E. hirta* is naturally distributed in Fujian, Guangdong, Guangxi, Guizhou, Hainan, Hunan, Jiangxi, Sichuan, Taiwan, and the Yunnan regions (Flora of China). Recently, modern pharmacological investigations showed that *E. hirta* and its active components possessed wide pharmacological actions, such as anti-inflammatory, antifungal, antibacterial, antidiarrheal, sedative, anxiolytic, analgesic, antipyretic, antioxidant, antiasthmatic, antitumor, antimalarial, larvicidal, diuretic, and increases electrolytes, among others (Lanhers et al, 1990; Lanhers et al, 1991; Johnson et al, 1999; *Euphorbiahirta* L. Available: <http://florabase.dec.wa.gov.au/browse/profile.php/4629>).

Most of its pharmacological actions are in line with the traditional efficacy. On the other hand, *E. hirta* is also used as a livestock fodder worldwide. The chemical components of *E. hirta* along with its pharmacological actions have been studied by various laboratories. Flavonoids,

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terpenoids, and phenols were isolated and identified as the main compositions of *E. hirta*.

In the current paper, an overview of the current knowledge and information about *E. hirta* is presented for the study of its ethnopharmacology, phytochemistry, pharmacology, and toxicology.

BOTANY AND ETHNOPHARMACOLOGY

According to the description from Flora of China and Zhonghuabencao [Zhong hua ben cao, 1999; Flora of China, 1987], *E. hirta* is a small annual, branched herb prostrate to ascending with branches reaching 70 cm in height, reddish or purplish in color, with abundant latex and is covered with short hairs. Its leaves are opposite, distichous, and simple; its obvious stipules are linear. The leaf blades of *E. hirta* are lanceolate-oblong, long elliptic, or ovate-lanceolate; its base is very unequal; one side is cuneate, the other side is round; the apex is almost acute, and its margins are finely toothed, often with a purple blotch near the midvein. The inflorescence of *E. hirta* has a terminal or axillary cluster of flowers, called a 'cyathium', with several cyathia densely clustered into a cyme. The flowers of *E. hirta* are unisexual; the male flowers are sessile, the bracteoles are linear, fringed, the perianth is absent, and possesses one stamen, whereas the female flowers have short pedicel, the perianth is rimmed, the ovary is superior, covered with short hairs, three-celled, possesses three styles, minute, and the apex is two-fid. The fruit of *E. hirta* is exerted, acutely three-lobed, base truncate, covered in short hairs, and three-seeded. The seeds are oblong, four-sided prismatic, slightly wrinkled, pinkish brown, and caruncle absent. Flowering duration of individual plant is usually throughout the year. *E. hirta* often grows in cultivated areas in lowland, paddy fields, gardens, roadsides, and waste places. They prefer dry condition, from sea-level up to 2000 m altitude.

E. hirta has many synonyms in different countries. In China, it is called Feiyangcao, Dafeiyang, Jiejiehua, and Daruzhicao. The following are its other synonyms. Malaysia: Ambin jantan, kelusan; English: Asthma herb, hairy spurge; Indonesia: Daun biji kacang (Malay. Moluccas), nanangkaan (Sundanese); Papua New Guinea: Sip (Kurtatchi. Bougainville), kiki kana kuku (Gunantuna, New Britain); Philippines: Botobotonis (Tagalog), gatas-gatas (Bisaya, Tagalog); Laos: Mouk may, ungl yang; Thailand: Nam nomraatchasee (central), yaa nam muek; Vietnam: C[or]s[uwx]ra, C[or]s[uwx]al[ows]nl[as]; French: Euphorbea fleusentete, euphorbepilulifere; India: Dudhi, reddinanabrolu; Bangladesh: Bara Keru, Ghaopata; Norway: Demba sindji; Australia: Asthma plant; and Liberia: tuagbono.

E. hirta has a long history as a medicinal herb in China. Different formulations are used, including crude drug, decoction, infusion, lotion, and powders. *E. hirta* plays a

very important role in TCM, especially in folk medicine because of its wide range of biological and pharmacological properties.

Considering the effects of *E. hirta* on curing skin ulcer and swelling of body, it was first recorded in "Ling Nan Cai Yao Lu". More than ten folk medicinal books in China also have recorded this plant (Yin, 2008; Liang and Zhong, 2005; Zhu et al., 2007; He and Ma, 2006). The whole plant was officially recorded in a Chinese Pharmacopoeia (1977). However, *E. hirta* had been removed from the 1985 to 2005 edition, and have been re-listed as Feiyangcao in the Pharmacopoeia edition of 2010. The Pharmacopoeia stated the properties of *E. hirta* that cure fever, detoxify, promote diuresis, stop itching and induces prolactin. The clinical indications include pulmonary abscess, acute mastitis, diarrhea, eczema, furunculosis, pyogenic infections, and postpartum milk. The fresh whole plant or its crude powders were also traditionally used as veterinary medicine for treating esenteritis, gastritis, diarrhea in pig, cattle, horse, sheep, and fish (The State Pharmacopoeia Commission of People's Republic of China, 2010).

E. hirta has also been widely used in medicine among minority groups, including Yao, Zhuang, Dai, Naxi, and Yi, who lived in the southern area of China. The Yao people use the entire plant for the treatment of bronchitis, external usage for scald and burned, decoction of dry plant, whereas as fresh crushed leaves are used to cure skin disease (Yin, 2008). For the Zhuang people, a decoction, infusion, or tincture of the plant is used to treat asthma, chronic bronchial disorders, and emphysema (Liang and Zhong, 2005). For Dai nationality, *E. hirta*, commonly known as Ya nan mo, is applied to stimulate milk secretion and to stopping cough (Zhu et al., 2007). Moreover, *E. hirta* is used to cure gonorrhoea and hematuria in Naxi people [He and Ma, 2006]. Therefore, *E. hirta* can be served clinically as potential hemostatic.

E. hirta is included in the African pharmacopoeia of the Organization of African Unity as a dysentery medication. In South Africa, *E. hirta* is commonly used for asthma treatment, which is one of the most common respiratory complaints [Ekpo and Pretorius, 2007]. In West Africa, *E. hirta* is used as a livestock fodder. In the Gold Coast, *E. hirta* was ground, mixed with water, and used as an enema for constipation. In traditional Indian medicinal systems, the leaves are used in the treatment of coryza, cough, asthma, bronchial infections, bowel complaints, helminthic infestations, wounds, kidney stones, and abscesses. In addition, it is used for the treatment of syphilis. The latex is applied to the eyes to treat conjunctivitis and corneal ulcerations. The tender shoots are used as famine food, raw or steamed, but they may cause intestinal complaints. Moreover, *E. hirta* is used by nursing mothers with deficient milk supply. In the Philippines, leaves are mixed with datura metel leaves and flowers in the preparation of "asthma-cigarettes." The

latex and fluid extract of the tincture are used in asthma, chronic bronchitis, emphysema, as well as in pulmonary cardiac disease and angina pectoris and ringworm. The decoction is used to allay the dyspnea of asthmatics. The decoction of the root is used to allay vomiting, chronic diarrheas, and fevers. Root decoction is also used for snake bites, sores, wounds, boils, and is beneficial for nursing mothers with deficient milk. The entire plant is prescribed as an antidote; it is considered hemostatic, sedative, and soporific. In Australia, the most common use of *E. hirta* is to treat hypertension, asthma, edema, and pectoral complaints.

PHYTOCHEMISTRY

E. hirta mainly contains flavonoids, terpenoids, phenols, essential oil, and other compounds. The major chemical structures of these compounds are shown in Figure 1.

One type of the important constituents of *E. hirta* is flavonoids including quercetin, quercitrin, quercitol, and derivatives containing rhamnose, quercetin-rhamoside, a chlorophenolic acid, rutin, leucocyanidin, leucocyanidol, myricitrin, cyanidin 3,5-diglucoside, pelargonium 3,5-diglucoside, and, camphol. The flavonol glycoside xanthorhamnin was also isolated from *E. hirta*. The stems contain the hydrocarbon hentriacontane and myricyl alcohol. The latex contains inositol, taraxerol, friedelin, β -sitosterol, ellagic acid, kaempferol, quercitol and quercitrin.

Another type of constituents of the aerial parts of *E. hirta* are terpenoids, including triterpenes: α -amyirin, β -amyirin, friedelin, taraxerol, and its ester: Taraxerone, 11 α , 12 α -oxidotaraxerol, cycloartenol, 24-methylene-cycloartenol, and euphorbol hexacosate. The aerial parts and roots of *E. hirta* also contain diterpene esters of the phorbol type and ingenol type, including 12-deoxyphorbol-13-dodecanoate-20-acetate, 12-deoxyporbol-13-phenylacetate-20-acetate, ingenol triacetate, as well as the highly toxic tinyatoxin, a resiniferonol derivative. Some new ent-kaurane diterpenoid were isolated from the ethanol extract of *E. hirta* and identified as 2-beta, 16-alpha, 19-trihydroxy-ent-kaurane, 2-beta, 16-alpha-dihydroxy-ent-kaurane, and 16-alpha, 19-dihydroxy-ent-kaurane (Yan et al., 2011). The other terpenoids isolated are sterols, including β -sitosterol, campesterol, cholesterol, and stigmasterol (Hazimi et al., 2008; Baslas and Agarwal, 1980).

Tannins isolated from *E. hirta* include the dimeric hydrolysable dehydroellagitannins 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-caffeoylquinic acid (neochlorogenic acid), and 3,4-di-O-galloylquinic acid, and benzyl gallate. Acids isolated from *E. hirta* include ellagic, gallic, tannic, maleic and tartaric

acids.

The major components of the essential oil include 3,7,11,15-tetramethyl-2hexadecen-1-ol, 6,10,14-trimethyl-2-pentadecanone, hexadecanal, phytol, and n-hexadecanoic acid adding up to 61.01%. The minor constituents of *E. hirta* include 2-butoxyethanol, tetradecane, phthalic acid, butyl tetradecyl ester, oleic acid, 13-heptadecyn-1-ol, 2-methyl-1-hexadecanol, and 1,2-benzene dicarboxylic acid diisooctylester. The component in essential oil may be responsible in the treatment of asthma and function as a repellent against Anopheles species, and thus, is useful for the treatment of malaria (Ogunlesi et al., 2009). The other compounds found in *E. hirta* are alkaloids, saponins, amino acid and mineral. The mineral content of a sample of the dried leaves was: Ca 1.1%, P 0.3%, Fe 0.03%, Mg 0.5%, Mn 0.01%, Zn 0.01%, and Cu 0.002%. Fresh leaves from *E. hirta* plants of Nigerian origin were found to contain high levels of Mn (189 ppm), Cu (30.5 ppm), Zn (152 ppm), and NO₃ (4600 ppm). Varying proportions of Fe, Mg, K, Ca, and Na were also found. More recently, two novel butanol rhamnopyranosides (1 and 2), have been isolated from various non-polar and polar extracts of an Indian traditional herb, *E. hirta*. The structures of the new compounds were elucidated as n-butyl-1-O--L-rhamnopyranoside (1) and n-butyl-1-O--L-rhamnopyranoside (Mallavadhani and Narasimhan, 2009).

PHARMACOLOGICAL PROPERTIES

Antibacterial/antifungal activity

Since the 1980s, the antibacterial activity of *E. hirta* has been comprehensively investigated and proven. Vijaya et al. [1995] evaluated the antibacterial potential of the methanol extract of *E. hirta* in 1995. Results showed that the extract exhibited properties against dysentery causing *Shigella* spp. using the Vero cell line. 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. The extracts were found to be non-cytotoxic and effective antibacterial agents.

Jackson et al. (2009) evaluated the antimicrobial activity of nystatin and the methanol extract of the leaves of *E. hirta* against *Candida albicans* using the checkerboard method. The results showed that some combinations of the extract with nystatin could be synergistic in activity for some ratio combinations and similar for some others.

The antimicrobial activity of ethanol extracts of the aerial parts of *E. hirta* was then investigated. A remarkable antimicrobial effect has been revealed against *Escherichia coli* (enteropathogen), *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The diameters of inhibition zones were 21, 19, 23, and 19

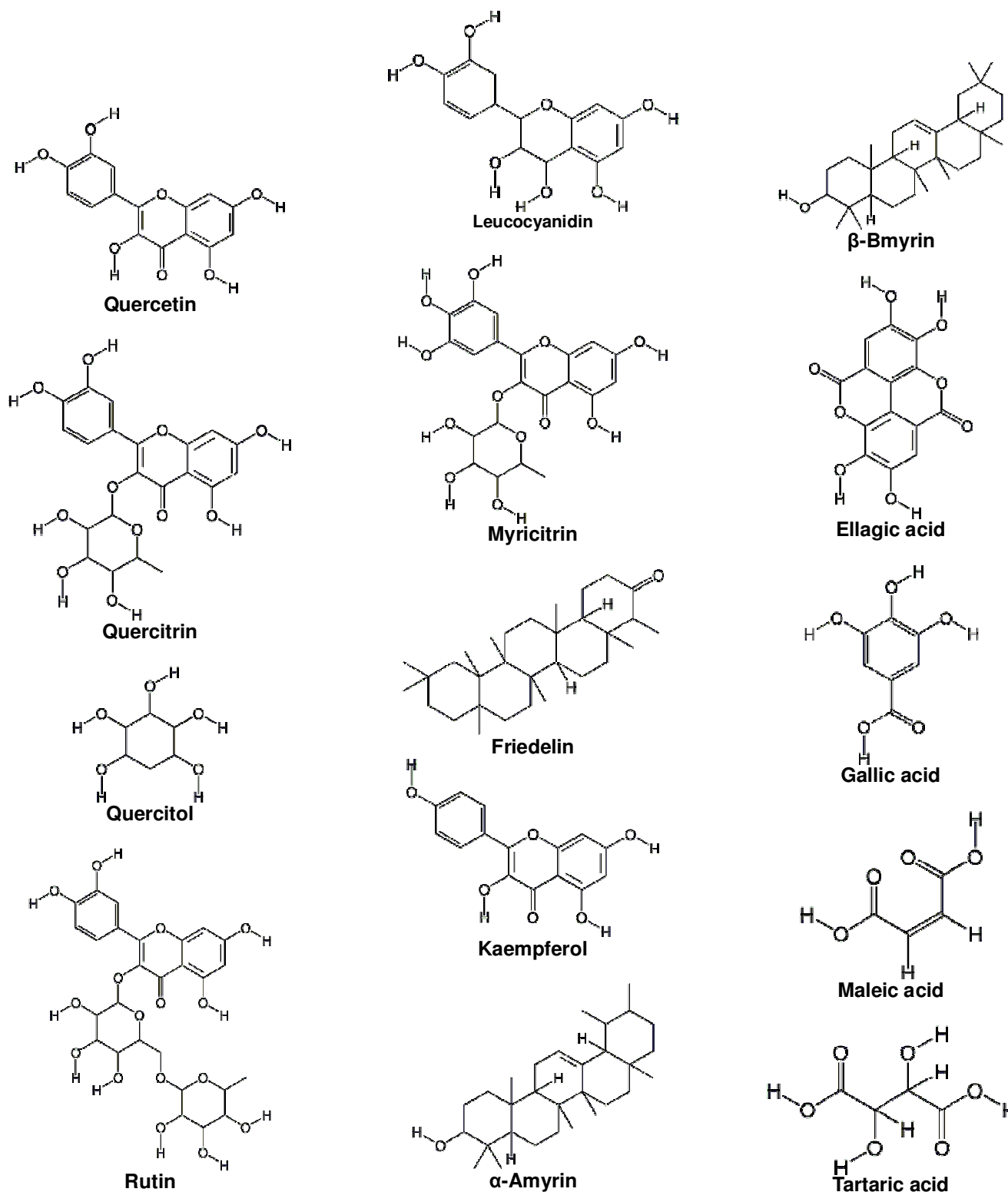


Figure 1. The structure of main compounds from *E. hirta*.

mm, respectively. The MIC values were 0.189, 0.2, 0.166, and 0.216 mg/ml [Sudhakar et al., 2006]. The ethanol

extract from the leaves of *E. hirta* was analyzed for antimicrobial activity against *S. aureus*, *Bacillus cereus*,

Salmonella typhi, *Klebsiella pneumoniae*, *P. aeruginosa*, and fungus species *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, and *Rhizopus oryzae*. Antimicrobial activity was attributed to tannins, flavonoids, alkaloids, glycosides, proteins, sterols, and saponins. Moreover, leaves collected from August to December showed more significant antimicrobial activities [Suresh et al., 2008].

Meanwhile, the crude ethanolic extract of *E. hirta* also showed marked antibacterial activity against the growth of *E. coli*, *S. aureus*, *P. aeruginosa*, and *Bacillus subtilis* [Ogbulie et al., 2007]. Nelofar et al. (2006) compared the antibacterial activity of the ethanol extract of *E. hirta* between Gram positive and Gram negative organisms, and results showed that the extract is more active against Gram positive organisms than Gram negative bacteria. An ethanolic extract of *E. hirta* showed an antifungal activity against the plant pathogens *Colletotrichum capsici*, *Fusarium pallidoseum*, *Botryodiplodia theobromae*, *Phomopsis caricae-papayae*, and *A. niger* using the paper disc diffusion technique [Mohamed et al., 1996]. Meanwhile, Akinrinmade and Oyeleye, (2010) investigated the efficacy and tissue reaction of the crude ethanolic extract of *E. hirta* in canine infected incised wounds. The results showed that the crude ethanolic extract of *E. hirta* neither promoted the growth of *S. aureus*, nor provoked tissue reaction in canine wounds, thus, it was recommended for use in surgical site preparation. Abubakar (2009) compared the antibacterial capability of the methanol, hexane, and water extract of *E. hirta* in *E. coli*, *K. pneumoniae*, *Shigella dysenteriae*, *S. typhi*, and *Proteus mirabilis*, a group of Gram-negative bacteria that frequently cause enteric infections in humans. The results showed that the water extracts provided more antibacterial effectiveness than organic solvent extracts. Phytochemical screening of the crude extracts revealed the presence of tannins, saponins, phenolics, flavonoids, cardiac glycosides, anthroquinones, and alkaloids. These bioactive constituents have been linked to antimicrobial activity.

Finally, Mohammad Abu Basma Rajeh assessed the potential antimicrobial activity of *E. hirta* leaves, flower, stem, and root extracts using a broad arrange of microbial samples, including four Gram positive bacteria (*S. aureus*, *Micrococcus* sp., *B. subtilis*, and *Bacillus thuringensis*), four Gram negative bacteria (*E. coli*, *K. pneumoniae*, *S. typhi*, and *P. mirabilis*), and one yeast (*C. albicans*). Inhibition zones ranged between 16 and 29 mm. Leaf extract inhibited the growth of all tested microorganisms with large zones of inhibition, followed by that of the 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 with the stem extract. The

lowest MIC values were obtained for *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 other bacteria had MIC values of 100.00 mg/ml [Mohammad et al., 2010]. The results support the use of *E. hirta* in traditional medicine.

Anti-allergic activity

The ethanolic extract of *E. hirta* was found to possess a prominent anti-anaphylactic activity. *E. hirta* inhibited passive cutaneous anaphylaxis (PCA) in rat and active paw anaphylaxis in mice. The suppressive effect of *E. hirta* was observed on the release of TNF- α and IL-6 from anti-DNP-HAS activated rat peritoneal mast cells. The findings of the current study prominently validate the traditional use of *E. hirta* as a herbal drug against Type I allergic disorders [Youssof et al., 2007]. The current study demonstrated that 90% of the ethanolic extract from the whole aerial parts of *E. hirta* possessed significant activity to prevent early and late phase allergic reactions caused by antihistaminic, antiinflammatory, and immunosuppressive properties. Moreover, the ethanolic extract of *E. hirta* can prevent and treat rat anaphylactic [Youssof et al., 2007; Singh et al., 2006].

Antidiarrheal activity

The aqueous leaf extract of *E. hirta* significantly and dose-dependently decreased the gastrointestinal motility in normal rats and decreased the effect of castor oil-induced diarrhea in mice [Hore et al., 2006]. The antidiarrheal effect of the *E. hirta* herb decoction was studied in mice. It demonstrated an activity in models of diarrhea induced by castor oil, arachidonic acid, and prostaglandin E₂. Quercitrin, a flavonoid isolated from this crude drug contributed to the antidiarrheal activity at a dose of 50 mg/kg, against castor oil and prostaglandin E₂-induced diarrhea in mice [Galvez et al., 1993, 1993]. The water extract of *E. hirta* exhibited antidiarrheal, antibacterial, antiamebic, and antitetanitic properties. The polyphenolic extract of *E. hirta* inhibited the growth of *Entamoeba histolytica* with a minimum active concentration of less than 10 mg/ml [Tona et al., 2000].

Anti-inflammatory activity

In 1991, Lanhers et al. (1991) has proven that the aqueous extract of *E. hirta* had significant and dose-dependent anti-inflammatory effects in carrageenan-induced edema test in rats (an acute inflammatory process) from a dose of 100 mg/kg. Martinez et al. (1999) evaluated the anti-inflammatory effect of the n-hexane

extract of the aerial parts of *E. hirta* and its main triterpene constituents. The results showed that the extract and chemicals reduced the inflammatory hyperalgesia in a dose-dependent manner and displayed significant anti-inflammatory effects in the model of phorbol acetate-induced ear inflammation in mice. In 2007, Ekpo OE and Pretorius, evaluated the anti-inflammatory activity of the chemicals in *E. hirta* and concluded that the flavonoids quercitrin (converted to quercetin in the alimentary canal) and myricitrin, as well as the sterols 24-methylene-cycloartenol and -sitosterol, exert noteworthy and dose-dependent anti-inflammatory activity. Triterpene beta-amyrin also seems to exert a similar anti-inflammatory activity [Ekpo and Pretorius, 2007]. Shih et al 2010, elucidated the underlying pharmacological molecule mechanism of action in alleviating inflammation. The anti-inflammatory activity of the extract of *E. hirta* and its active components were studied in lipopolysaccharide (LPS)-activated macrophage cells (RAW264.7) as an established inflammation model. After activation, nitric oxide (NO) production and expression of iNOS protein and iNOS mRNA were measured using colorimetric assay (Griess reagent), western blot analysis, and reverse transcription polymerase chain reaction (RT-PCR), respectively. The alteration in the content of PGE₂, TNF α , and IL-6 was concurrently monitored using enzyme-linked immuno-sorbent assay (ELISA). The results showed that the ethanol extract of *E. hirta* and its component beta-amyrin produced a remarkable anti-inflammatory effect, and are able to block most of the iNOS protein functions and NO induction, presenting a great potential as a new selective NO inhibitor for the treatment of arthritis inflammation [Shih et al., 2010].

Diuretic activity

Johnson et al. (1999) has found that the ethanolic and aqueous leaf extracts of *E. hirta* could significantly induce diuresis in rats. It increased urine output and electrolytes. The diuretic effect of the ethanol extract was obvious at 6 h (for 100 mg/kg) and at 24 h (for 50 mg/kg) in a time-dependent manner. The water extract significantly increased the urine excretion of Na⁺, K⁺, and HCO₃⁻, whereas the ethanol extract (100 mg/ml) caused a significant decrease in K⁺. The HCO₃⁻ urine output following the injection of both extracts was remarkably enhanced. Studies suggested that the active components in the water extract of *E. hirta* leaf had similar diuretic effect as that of acetazolamide. The results validate the traditional use of *E. hirta* as a diuretic agent by the Swahilis and Sukumas of East Africa [Johnson et al., 1999].

Antioxidant activity

The methanol and water extracts of *E. hirta* showed

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. These techniques also investigated the protective potential of identified antioxidants against oxidative injury to BSA with the help of sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblot techniques using anti-DNP primary antibody. These groups of phenolic acids possessed significant antioxidant activities. Phenolic acids demonstrated synergistic interaction with BSA, and their antioxidant activity was found to be enhanced after incubation with BSA to 20%. Different analytical methods, including DNPH, fluorescent quenching, SDS-PAGE, and immunoblot analysis supported and complemented the same research findings. The results substantiated the significant contribution of phenolic acids with an effective value, EC₅₀, of 150 g/ml in protection against oxidative injury to Phosphate Buffered Saline (PBS). The phenolic acid from *E. hirta* displayed enhanced free radical scavenging activity, and showed a promising role in the protection against oxidative damage to protein.

In addition, the aqueous extract of *E. hirta* demonstrated an antioxidant effect and a free radical scavenging effect in various *in vitro* models, such as total antioxidant and total ferric reducing power determination, free radical-scavenging activity assay using ABTS, DPPH, and hydroxyl radical scavenging assays. The extract showed maximum antioxidant and free radical scavenging activities, at the concentration of 0.25 mg/ml. The free radical scavenging effect on hydroxyl and DPPH was 73.36 ± 5.21 and $68.80 \pm 5.21\%$, respectively (Sharma et al., 2007). The free radical scavenging effect of ethanolic extract and petroleum ether extracts of the flower of *E. hirta* was also evaluated through various *in vitro* antioxidant assays, including 1,1-diphenyl-2-picryl hydrazyl free radical scavenging activity, superoxide anion radical scavenging, NO scavenging, and reducing power assay. It was compared with standard antioxidant compounds, such as butylated hydroxyl anisole and ascorbic acid. All the extracts showed antioxidant activity (Kumar et al., 2010).

Finally, the antioxidant activity from different parts of *E. hirta* (leaves, stems, roots, and flowers) has been studied by Abu et al. (2011). Samples of leaves, stems, flowers, and roots from *E. hirta* were tested for total phenolic content, flavonoid content, and *in vitro* antioxidant activity using DPPH assay, and the reducing power was measured using the cyanoferrate method. DPPH assay and reducing power was measured using the cyanoferrate method. The results showed that the leaf extract exhibited a maximum DPPH scavenging activity of 72% followed by

the flowers, roots, and stems with scavenging activity values of 52, 48, and 44%, respectively. The standard butylated hydroxytoluene (BHT) was 75%. The IC₅₀ for leaves, flowers, roots, stems, and BHT were 0.803, 0.972, 0.989, 1.358, and 0.794 mg/ml, respectively. Leaf extracts had the highest total phenolic and total flavonoid content, followed by the flower, root, and stem extracts. The results suggested that *E. hirta* exhibited strong antioxidant activity and can serve as a new antioxidant agent using various *in vitro* anti-oxidant tests.

Anti-tumor activity

The antitumor activity of the aerial part of *E. hirta* was evaluated against EL-4 cell line (S.C.) in Swiss albino mice. A significant enhancement of mean survival time and reduction of solid tumor mass of EF-treated tumor-bearing mice was observed (Sandeep and Chandrakant, 2011). The methanol extract of the leaves of *E. hirta* on Hep-2 cells from human epithelioma of the larynx showed anti-proliferative activity (Brindha et al., 2010). Daphne et al. (2009) evaluated the mutagenic and antimutagenic activities of the aqueous and methanolic extracts and quercetin from *E. hirta*. The aqueous extract (100 g/ml) and methanolic extract (10 and 100 g/ml) demonstrated the mutagenicity of 2-aminoanthracene in *S. typhimurium* TA98 in the presence of S-9 metabolic activation. Quercetin was proven to be mutagenic and did not show any antimutagenic activity in the absence and presence of S-9 metabolic activation in *S. typhimurium* TA98. The findings indicate that the aqueous and methanolic extracts of *E. hirta* is a potential anti-carcinogenic agent.

Anti-diabetic activity

The antidiabetic activity of the ethanol and ethyl acetate extracts of *E. hirta* was assayed *in vitro* using the alpha glucosidase inhibitor method and confirmed through *in vivo* oral glucose tolerance test using various loading methods. Several mechanisms may be involved in the process, including the antioxidant activity, α -glucosidase inhibitory activity, and increasing the activity of insulin release form β cells of the Langerhans islets. The study of ethanolic extracts of leaf, flower, and stem of *E. hirta* on streptozotocin-induced diabetic mice showed significant reduction in blood glucose levels. Biochemical effects showed significant decreases in serum cholesterol with the elevation of HDL (Widharna et al., 2010). The ethanolic and petroleum ether extracts of the flower of *E. hirta* also demonstrated potential antidiabetic mellitus activities in alloxan diabetic mice. A significant reduction in serum cholesterol, triglycerides, creatinine, urea, and alkaline phosphatase levels were observed after the

administration of the extract. However, high density lipoprotein levels and total proteins were found to increase (Kumar et al., 2010).

Anxiolytic and sedative activity

The hydroalcoholic extract of *E. hirta* was evaluated for anxiolytic property in chronically stressed rats subjected to two different stressors: Chronic immobilization stresses (CIS) and forced swim stress (FSS). The anxiety in the elevated plus maze (EPM) and the open field test (OFT) was assessed. To understand the mechanism underlying the anxiolytic action of this drug, antagonists of the GABAA receptor-benzodiazepine receptor-Cl₋ channel complex with *E. hirta* were co-administered, and anxiety in the EPM was evaluated. The findings clearly demonstrate the anxiolytic potential of *E. hirta*, particularly in CIS induced anxiety. The actions of *E. hirta* could be mediated, at least in part, through the GABAA receptor-benzodiazepine receptor-Cl₋ channel complex (Anuradha et al., 2008). Lanhers et al. (1990) also investigated the behavioral effects of the aqueous extract of *E. hirta* in mice. The results displayed sedative and anxiolytic properties, which validate the traditional use of *E. hirta*. *E. hirta* showed an activity profile different from that of benzodiazepines. The current study showed a central depressant and sedating effect with no hypnotic or neuroleptic effects, and validated the traditional use of *E. hirta* as a sedative with anxiolytic properties.

Other activities

Antihypertensive / ACE inhibition

Angiotensin-converting enzyme inhibition and anti-dipsogenic activities of *E. hirta* extracts: The current study showed that the extract from leaves and stems of *E. hirta* inhibited the activity of angiotensin-converting enzyme (ACE).

Anthelmintic and larvicidal activity

The crude aqueous extract of *E. hirta* reduced the fecal egg count of the helminths in Nigerian dogs and exhibits a potential as an anthelmintic agent. At the same time, the aqueous stem bark and leaf extract of *E. hirta* significantly decreased the level of nucleic acids in various tissues of the vector snail, and are potential inhibitors of DNA synthesis, resulting in the reduction of the RNA level. The current study indicated that the plant extract possess great value for the control of aquatic harmful vector snail organisms (Sunil et al., 2005).

Preeti et al. (2009) highlighted the larvicidal property of

the three forms of extracts of *E. hirta* against the third instar larvae of *Anopheles stephensi*, the urban malaria vector. Petroleum ether extract has the lowest LC50 values at 9,693.90 and 7,752.80 ppm after a 24- and 48-h exposure period followed by carbon tetrachloride extraction (IC50 11,063.00 and 10,922.00 ppm after 24 and 48 h of exposure), and methanol extract (the LC50 values are 19,280.00 and 18,476.00 ppm after 24 and 48 h of exposure). The current study reflects that the larvicidal potency of petroleum ether extracted fractions could be a promising insecticide of botanical source. Moreover, the latex of *E. hirta* may be considered as a plant derived molluscicide agent against freshwater snails (Yadav and Singh, 2011).

Anti-malarial

In the study of the isolated flavonol glycosides afzelin, quercetin and myricitrin, the three compounds showed inhibition of the proliferation of *Plasmodium falcifarum* at different concentrations (Koli et al., 2002).

Immunomodulatory activity

In 2001, the whole plant of *E. hirta* has been reported to possess 45% immunomodulation activity through the inhibition of NO production (Jae-Ha et al., 2001). Ramesh and Vijaya, (2010) reported the *in vitro* and *in vivo* immunomodulatory properties of *E. hirta*, which has been proven through macrophage activity testing, carbon clearance test, and mast cell de-granulation assay. The aqueous extract of the leaves of *E. hirta* Linn could serve as an immunostimulant on the experiment of the pathogen-infected *Cyprinus carpio* Linn. (Cyprinidae). The higher concentration of the extract (50 g/kg diet) provided significant immune response (specific and nonspecific) on the fish. The 50 g/kg leaf extract of *E. hirta* enhanced the phagocytic ratio on the 10th and 15th day after infection. The findings will help the researchers for the discovery of significant aquaculture nutrients to improve its immunostimulant action on fish (Pratheepa and Sukumaran, 2011).

TOXICOLOGY

E. hirta has been used as a traditional herbal medicine for years worldwide. However, it contains some properties that may be slightly toxic. Unfortunately, the study of the relative systematic toxicity and safety evaluations of *E. hirta* have been lacking, and only few reports of target-organ toxicity or side effects have been documented in literature. The aqueous crude extracts of *E. hirta* were administered orally to a 38-week old mature male at the

dose of 400 mg/kg to determine the effects of the extracts on the male reproductive organs. The results revealed that the extract caused varying degrees of testicular degeneration and reduction in the mean seminiferous tubular diameter (STD) in the treated rats. Thus, *E. hirta* have potentially deleterious effects on the tested and accessory organs of rats (Adedapo et al., 2003).

As previously described, the aqueous stem, bark, and leaf extracts of the *E. hirta* have potent molluscicidal activity. The sub-lethal doses of the extract (40 and 80% of LC50) also remarkably ($p < 0.05$) altered the levels of total protein, total free amino acid, and nucleic acids (DNA and RNA), and the activity of enzyme protease, acid, and alkaline phosphatase in various tissues of the vector snail *Lymnaea acuminata* in time and dose dependent manners (Sunil et al., 2005). Mohammad et al., (2010) evaluated the toxicity of *E. hirta* extract using brine shrimp lethality assay. The results showed that all the parts of *E. hirta*, except the flower extract, had LC50 values of almost 1000 ug/ml. Therefore, great caution should be taken when consuming this plant as medicinal agents and a safety dosage must be considered as well.

CONCLUSION

E. hirta is a popular herb among practitioners of traditional herb medicine in China and other counties and areas, such as Africa, India, Philippines, Australia, and Cambodia. It has long been used as a decoction or infusion for the treatment of various ailments, particularly intestinal disorders, diarrhea, amoebic dysentery, peptic ulcers, asthma, bronchitis, and skin diseases in China. However, in Australia, one of the most popular uses of *E. hirta* is for the treatment of hypertension. In Java and India, the tender shoots, raw or steamed, serve as famine food. In Philippine Medicinal Plants, people even use the entire plant of *E. hirta* for tea-making. Hence, there are versatile traditional usages among different regions. Since *E. hirta* is widely distributed in pan-tropic and partly subtropic areas, it may form distinct ecotypes in different habitats and possesses distinct chemical profiles. Further detailed investigation is needed to clarify this phenomenon.

Currently, various compounds have been isolated and identified from *E. hirta*, among which, flavonoids, terpenoids, and phenols are the major constituents. These monomeric compounds and crude extracts from *E. hirta* have been screened for pharmacological activities *in vivo* and *in vitro*. Various experimental studies validated the traditional medicinal uses of *E. hirta*. However, the intrinsically active compounds and the chemical responsible have been determined yet, and some mechanisms of the action of *E. hirta* are still unknown. Thus, bioassay-guided isolation and identification of the bioactive components must be developed to reveal the structure-activity relationship of these active components.

Moreover, the major constituents and important chemotaxonomic markers are still ambiguous, and there is no indicator compound to characterize the quality of *E. hirta* and the preparations in Chinese Pharmacopoeia (2010 edition). Thus, an exclusive and accurate evaluation of the quality of *E. hirta* in crude herbal materials and preparations should be investigated further.

Several parts of the plant have interesting antidiabetic, anti-tumor, anti-oxidant and antimicrobial properties. Consequently, further studies on this plant should be considered by researchers in phytochemistry and pharmacology in discovering newer and potential bioactive compounds such as antidiabetic, antioxidants and anticancers.

ACKNOWLEDGEMENTS

The authors thank key national natural science foundation of China (81130069), Chinese Pharmaceutical Industry R & D Project (No. 200707007) and the State Key Laboratory of Traditional Chinese Medicine Resources research and development in Chendu University of TCM for providing financial assistances.

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