Asthma, *Euphorbia hirta* and its anti-inflammatory properties

O.E. Ekpo* and E. Pretorius*‡

EUPHORBIA HIRTA IS A PLANT USED IN TRADITIONAL medicine for a variety of diseases, such as cough, asthma, colic dysentery and genito-urinary infection. This plant, belonging to the family *Euphorbiaceae*, is also known as the Australian asthma herb or Queensland asthma weed, and is not toxic when taken in typical dosages. In South Africa, it is commonly used for asthma, which is one of the most common respiratory complaints. Although corticosteroids are considered the best means of defence against this debilitating illness, many people, especially in poor countries, rely on herbal remedies for its treatment. We discuss recently published results to assess the effect of the plant using the BALB/c murine asthma model. We also review the different compounds found in plant extracts, in an attempt to understand the reason for its anti-inflammatory properties. We conclude 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. The triterpene β-amyrin also seems to exert a similar anti-inflammatory activity. Tannins and tannic acid derivatives, also present in the plant, have antiseptic effects and the two triterpenoids, taraxerone (EH-1) and 11α, 12α-oxidotaraxerol (EH-2), in *E. hirta* demonstrate antibacterial and antifungal properties. The effectiveness of *E. hirta* in treating asthma may lie predominantly in the synergistic relationships between the flavonoids, sterols and triterpenoids.

*Department of Anatomy, Faculty of Health Sciences, University of Pretoria, P.O. Box 2034, Pretoria 0001, South Africa.
‡Author for correspondence.
E-mail: resia.pretorius@up.ac.za

Introduction

Asthma is one of the most common respiratory complaints in the world today. It affects an estimated 300 million people worldwide, of whom about 50 million live in Africa, 15 million in the U.S., 5 million in the U.K. and 2 million in Australia.[1,2] Ten per cent of asthma sufferers are children and 5% are adults. Asthma mortality in the United States amounted to some 5000 persons in the year 2000. The global prevalence of the disease is expected to rise to 400 million by the year 2025.[3]

Most of the available pharmacological therapies simply control the known mechanisms by which the disease occurs. There is no complete cure for asthma. Pharmaceutical products have been the main source of anti-asthma treatment but some of these have recently been associated with serious adverse effects.

It is estimated that there are about 27 million consumers of indigenous medicine in southern Africa, a large number of whom consult traditional healers for potentially life-threatening conditions.[4,5] An estimated 60% of the South African population is reported to consult traditional healers.[6] Moreover, the steady increase in incidence of asthma has, as with any chronic condition, opened up a new era where sufferers are resorting to alternative treatments.[7]

One of the herbs used against asthma in southern Africa is *Euphorbia hirta* (family *Euphorbiaceae*), also known as the Australian asthma herb or Queensland asthma weed, cat's hair, hairy spurge, spurge or milkweed. In India, the plant is used for

Table 1. Summary of mean white blood cell counts in blood smears obtained from control group, asthmatic mice, asthmatic mice treated with low and high hydrocortisone (HC) doses, as well as asthmatic mice treated with *Euphorbia hirta* (5 areas from each blood smear, and 5 smears from each individual mouse, were counted; there were 6 mice per group).

	Control group	Asthma group	Low HC (100 mg/kg)	High HC (125 mg/kg)	*E. hirta* (0.01 ml of 62.5 mg/kg plant material)
Neutrophil	39	336	36	91	31
Eosinophil	13	104	10	3	4
Basophil	7	58	3	2	1
Lymphocyte	144	1203	41	81	82
Monocyte	203	737	32	63	113

treating a variety of diseases, such as cough, asthma, colic dysentery and genito-urinary conditions.[8–13] In East and West Africa, extracts of the decoction of the flowering and fruiting plants are used in the treatment of asthma and respiratory tract infections and are sometimes combined with bronchial sedatives such as *Grindelia robusta* in preparations for inhalation.[14,15] The plant is also employed in the treatment of coughs, chronic bronchitis and pulmonary disorders, especially in Australia.[16]

Since this plant is used as herbal medicine and is not cytotoxic when taken in typical amounts, Pretorius and co-workers investigated its effect in the treatment of asthma.[17] The BALB/c murine asthma model was used to investigate the consequences for mice exposed to low-dose hydrocortisone (HC) (100 mg/kg), mice exposed to higher-dose HC (125 mg/kg), and mice subjected to physiologically comparable levels of *E. hirta* (0.01 ml of 62.5 mg/kg plant material).

White blood cell counts are a reliable measure of asthmatic status. The process of inflammation in asthma is viewed as an inflammatory cascade, which is divisible into seven phases: sensitization, stimulation, cell signalling, migration, cell activation, tissue stimulation or damage, and resolution. In humans, eosinophil numbers are elevated in the airways of asthmatics and these cells release basic proteins and growth factors that may damage airway epithelial cells, and cause airway remodelling.[18] Additionally, neutrophil population is usually found to increase in the airways and in sputum of patients with severe asthma. It is therefore useful to examine these counts, to determine if an anti-asthmatic product is effective, particularly when compared with results from exposure to hydrocortisone (which, in our case, was used as a positive control) and reduces white blood counts in asthma. Table 1 shows that the mice in the asthmatic group (made asthmatic and not treated with any product) met the criteria for an asthmatic state. Both doses of hydrocortisone lowered the white blood counts in the mice, as did the plant extract. The neutrophils, eosinophils and basophils specifically were also lowered; these cells are known to be active in inflammation.

Platelets and fibrin networks also play a fundamental role in asthma. Pretorius and co-workers showed that control mice possess major thick fibres and minor thin fibres as well as tight round platelet aggregates with typical pseudopodia formation.[17] Minor fibres of asthmatic mice have a net-like appearance, covering the major fibres, whereas platelets appear to form loosely connected, granular aggregates. Both concentrations of hydrocortisone made the fibrin more fragile, and platelet morphology changed from a tight platelet aggregate to a more granular assembly, not closely fused to one another. Furthermore, it was claimed in the article that *E. hirta* does not influence the fragility of the fibrin and that it prevents the minor fibres forming the dense net-like layer over the major fibres, as is observed in untreated asthmatic mice. Furthermore, it seems that *E. hirta* does not render the fibrin fibres as fragile as is found with the HC-treated mice and it also does not alter the integrity and morphology of the platelets as was found in HC-treated mice. An important result is that *E. hirta* reduces inflammatory cells to the same level as that achieved by hydrocortisone, suggesting that the plant, indeed, has anti-inflammatory properties.

The question that now arose is, what components give the plant these properties? A review of the relevant available literature now follows.

Chemical compounds of *Euphorbia hirta*

Phytochemical analyses of *E. hirta* reveal flavonoids, sterols, tannins and triterpenoids in the bark and leaves.

Flavonoids

Two flavonoids have been isolated from *E. hirta*, namely quercitrin and myricitrin.[8,19] In general, flavonoids have been reported to possess several proven medicinal properties including anti-inflammatory, antioxidant, anti-allergic, antibacterial and antiviral activity.[6] The most abundant flavonoid in *E. hirta* is quercetin,[20,21] which has been reported to be the main agent that addresses the inflammatory component of asthma.[20] Flavonoids have been proposed to exert beneficial effects in many diseases, including asthma. Many of the biological actions of flavonoids have been attributed to their antioxidant properties, either through their reducing capacities or as a result of their possible influence on intracellular redox status.[22] Flavonoids can also interact selectively within the mitogen-activated protein (MAP) kinase signalling pathway.[22–24]

Possible anti-asthmatic effects of quercetin

Quercitrin (3-rhamnosylquercetin), found in *E. hirta*, is a bioflavonoid with antioxidant and anti-inflammatory properties.[25] It is converted in the alimentary canal to quercetin (3-*O*-α-L-rhamnopyranoside), which is the aglycone product of the former.[26–29] It is this converted product, quercetin, that is a potent anti-inflammatory chemical, and is believed to be the most important constituent in the plant responsible for the anti-asthmatic effects.

Sterols

Sterols that have been isolated from *E. hirta* and have been chemically characterized include cycloarternol, 24-methylene-cycloarternol, β-sitosterol, euphorbol hexacozonate, 1-hexacosanol, tinyaloxin, campesterol and stigmasterol.[8,29,30] The compounds 24-methylene-cycloartenol and β-sitosterol have also been found to exert significant and dose-dependent anti-inflammatory effects, when treating acetate-induced ear inflammation.[31]

Tannins and triterpenoids

Tannins are not widely known for their anti-inflammatory potential; *E. hirta* possesses a few such chemicals. Phytochemicals work synergistically, however, and therefore these tannins may assist in the anti-inflammatory action of the plant.

Euphorbia hirta presents three hydrolysable tannins, namely, dimeric hydrolyzable tannin, euphorbin E and the dimeric dehydroellagitannins, euphorbin A and euphorbin B.[32] Chen also isolated the following tannins from the leaves of *E. hirta*, using physicochemical and spectroscopic methods: gallic acid, 2,4, 6-tri-*O*-galloyl-D-glucose and 1,2,3,4,

Table 2. Chemical compounds isolated from *Euphorbia hirta.*

Flavonoids (flavonol glycosides)[8,19,20,21]	Quercitrin, isoquercitrin, myricitin
Tannins[32,19]	Dehydroellagitannins, euphorbin A, euphorbin B (isomer of euphorbin A), euphorbin E. Galloylglucoses: 2,4,6-tri-*O*-galloyl-D-glucose, 1,3,4,6-tetra-*O*-galloyl-β-D-glucose, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose, geraniin, 5-*O*-caffeoylquinic acid, 3,4-di-*O*-galloylquinic acid, gallic acid, ellagic acid, terchebin.
Triterpenoids[7,31,33]	α-Amerin, β-amyrin, β-amyrin acetate Taraxerone (EH-1), taxerol, 11α,12α-oxidotaraxerol (EH-2)
Sterols[8,29 31]	Cycloarternol (precursor in photosynthetic organisms), β-sitosterol, campesterol, stigmasterol, cycloarternol, 24-methylene-cycloarternol, euphorbol hexacozonate

6-penta-*O*-galloyl-β-D-glucose as well as the quinic acid ester, 3,4-di-*O*-galloylquinic acid.[19]

Research has shown that triterpenoids possess anti-inflammatory properties. The triterpenes α-amyrin, β-amyrin, taraxerone (EH-1), taxerol as well as β-amyrin acetate have been identified from *E. hirta*.[7,31,33] *N*-hexane extracts from the plant were found to contain β-amyrin, which displayed a significant and dose-dependent anti-inflammatory activity, when treating acetate-induced ear inflammation.[31] Two additional triterpenoids, namely, taraxerone and 11α, 12α-oxidotaraxerol (EH-2), have also been found in *E. hirta*.[34] These compounds induce both antibacterial and antifungal effects, as tested against fourteen pathogenic bacteria and six fungi.

Anti-inflammatory action of *E. hirta*

Table 2 shows the various components with anti-inflammatory properties that have been isolated from *E. hirta* thus far. Despite this variety of chemical compounds and the diverse local medicinal uses of the plant, it appears as if the flavonoids quercitrin and myricitrin are the compounds that induce the anti-inflammatory effect. However, the sterols, 24-methylene-cycloartenol and β-sitosterol,[31] and the triterpene, β-amyrin, also seem to display anti-inflammatory properties. Furthermore, tannins and tannic acid derivatives have antiseptic effects and the two triterpenoids, taraxerone and 11α, 12α-oxidotaraxerol, in *E. hirta*, also display antibacterial and antifungal properties.

These compounds in combination may have a synergistic effect, and may be the reason why *E. hirta,* as herbal medicine, has its claimed efficacy.

We thank the National Research Foundation for funding E.P. (Indigenous Knowledge Systems, FA2004033100004).

1. Masoli M., Fabial D., Holt S. and Beasley R. (2004). The global burden of asthma: Executive summary of the GINA Dissemination Committee Report. *Allergy* **59**, 469–478.
2. Kariyawasam H.H. and Robinson D.S. (2005). Airway remodeling in asthma: models and supermodels? *Clin. Exp. Allergy* **35**(2), 117.
3. Undem B.J. and Lichtenstein L.M. (2001). Drugs used in the treatment of asthma. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* eds J.G. Hardman and L.E. Limbird, pp. 733–754, 10th Int. Edn. McGraw-Hill, Whitby, Ontario.
4. Puckree T., Mkhize M., Mgobhozi Z. and Lin J. (2002). African traditional healers: what healthcare professionals need to know. *Int. J. Rehab. Res.* **25**, 247–251.
5. Mulholland D.A. and Drewes S.E. (2004). Global phytochemistry: indigenous medicinal chemistry on track in Southern Africa. *Phytochemistry* **65**, 769–782.
6. Van Wyk B-E., Van Oudtshoorn B. and Gericke N. (2000). *Medicinal Plants of South Africa,* 2nd edn. Briza, Pretoria.
7. Pinn G. (2001). Herbal therapy in respiratory diseases. *Aust. Fam. Physician* **30**(8), 775–779.
8. 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. *J. Ethnopharmacol.* **65**(1), 63–69.
9. Chopra R.N., Chopra I.C. and Verma B.S. (1969). Supplement to *Glossary of Indian Medicinal Plants,* pp. 63–64. CSIR, New Delhi.
10. Nadkarni K.M. (1976). *The Indian Material Medica,* Revised edition. Popular Prakhshan, Mumbai.
11. Kapoor S.L. and Mitra R. (1979). *Herbal drugs in Indian pharmaceutical industry,* 85 Economic Botany Information Service, National Botanic Research Institute, Lucknow, India.
12. Jain S.K. (1996). *Medicinal Plants,* 6th edn, pp. xiii and 178. National Book Trust, New Delhi.
13. Bhatnagar V.P., Anil K. and Srivastava J N. (2000). Wild medicinal herbs of Agra. *J. Med. Aroma. Plant Sci.* **22/4A**; **23/1A**, 464–467.
14. Oliver B. (1959). In *Medicinal Plants in Nigeria,* pp. 138–149. College of Arts, Science and Technology, Ibadan.
15. Kokwaro J.O. (1976). *Medicinal Plants in East Africa.* East African Literature Bureau, Nairobi.
16. Wong Ting-Fook. (1980). *Medicinal Plants of Mauritius.* ENDA Publications No.10. Dakar, Senegal.
17. Pretorius E., Ekpo O.E. and Smit E. (in press). Comparative ultrastructural analyses of platelets and fibrin networks using the murine model of asthma. *Experimental Toxicology and Pathology.*
18. Kay A.B., Phipps S. and Robinson D.S. (2004). A role for eosinophils in airway remodelling in asthma. *Trends Immunol.* **25**(9), 477–482.
19. Chen L. (1991). Polyphenols from leaves of *Euphorbia hirta* L. *Zhongguo Zhong Yao Za Zhi* **16**(1), 38–39, 64.
20. Miller A.L. (2001). The etiologies, patho-physiology and alternative/complementary treatment of asthma. *Altern. Med. Rev.* **6**(1), 20–47.
21. Skidmore-Roth L. (2001). *Mosby's Handbook of Herbs and Natural Supplements.* Mosby, St Louis, MO.
22. Williams R.J., Spencer J.P.E. and Rice-Evans C. (2004). Flavonoids: antioxidants or signaling molecules? *Free Radical Biol. Med.* **36**(7), 838–849.
23. 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. *Am. J. Physiol.* 277, C403–C411.
24. 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. *Arch. Pharm. Res.* 23, 1–16.
25. 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. *Br. J. Pharmacol.* **143**(7), 908–918.
26. Comalada M., Camuesco D., Sierra S., Ballester I., Xaus J., Galvez J. and 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. *Eur. J. Immunol.* **35**(2), 584–592.
27. 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. *Biochem. J.* **372**, 173–181.
28. Morand C., Manach C., Crespy V. and Remesy C. (2000). Respective bioavailability of quercetin aglycone and its glycosides in a rat model. *Biofactors* **12**, 169–174.
29. Galvez J., Crespo M.E., Jimenez J., Suarez A. and Zarzuelo A. (1993). Antidiarrhoeic activity of quercitrin in mice and rats. *J. Pharm. Pharmacol.* **45**(2), 157–159.
30. Atallah A.M., Nicholas H.J. (1972). Triterpenoids and steroids of *Euphorbia pilulifera. Phytochemistry* **2**, 1860–1868.
31. Martinez-Vazquez M., Apan T.O.R., Lazcano M.E. and Bye R. (1999). Anti-inflammatory active compounds from the n-hexane extract of *Euphorbia hirta. Rev. Soc. Quim. Mexico* **43**, 103–105.
32. Yoshida T., Namba O., Chen L. and Okuda T. (1990). Euphorbin E: A Hydrolysable tannin dimer of highly oxidized structure from *Euphorbia hirta. Chem. Pharmaceut. Bull.* (Tokyo) **38**, 1113–1115.
33. Ahmed A.M. and Nicholas H.J. (1972). Triterpenoids and steroids of *Euphorbia pilulifera. Phytochemistry* **11**, 1860.
34. 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 J. Sci. Ind. Res.* **48**(2), 122–125.