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Anti-inflammatory activities of *Emblica officinalis* Gaertn leaf extracts

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Abstract—*Emblica officinalis* Gaertn, a tree growing in subtropical and tropical parts of China, India, Indonesia and the Malay Peninsula, has been used for anti-inflammatory and antipyretic treatments of rural populations in these areas. In the present study, we examined the effects of *Emblica officinalis* extracts on carrageenan- and dextran-induced rat hind paw oedema. Anti-inflammatory activity was found in the water fraction of methanol extract of the plant leaves. The effects of the same fraction were tested on the synthesis of mediators of inflammation such as leukotriene B_4 (LTB_4), platelet-activating factor (PAF) and thromboxane B_2 (TXB_2), and on LTB_4- and *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP)-induced migration of human polymorphonuclear leucocytes (PMNs) in-vitro. The water fraction of the methanol extract inhibited migration of human PMNs in relatively low concentrations. It did not inhibit LTB_4 or PAF synthesis in human PMNs or TXB_2 synthesis in human platelets during clotting, suggesting that the mechanism of the anti-inflammatory action found in the rat paw model does not involve inhibition of the synthesis of the measured lipid mediators.

Emblica officinalis Gaertn, or in Malaysia, pokok Melaka, is a tree of small or moderate size with a greenish-grey bark and feathery leaves. It grows in tropical and subtropical parts of China, India, Indonesia and the Malay Peninsula. The Malaysian variety has more scurfy branchlets and the immature fruit is top-shaped. The name of Malacca, a river and town in Malaysia, is believed to have been derived from the name of this tree. Malays use a decoction of leaves to treat fever (Burkill 1966). In Indonesia, the pulp of the fruit is smeared on the head to dispel headache and dizziness caused by excessive heat (Perry 1980).

Leukotriene B_4 (LTB_4), a lipoxygenase product of arachidonic acid, is one of the mediators of inflammation. It is chemotactic and stimulates aggregation, adhesion, degranulation and superoxide production of human polymorphonuclear leucocytes (PMNs) in-vitro and in-vivo, and has been suggested to take part in the pathogenesis of different inflammatory diseases (for review, see König et al 1990). Cyclo-oxygenase pathway products of arachidonic acid such as prostaglandin E_2 (PGE_2), are also regarded as mediators of acute inflammation contributing significantly to the genesis of the inflammatory signs and symptoms (Moncada et al 1978). Thromboxane A_2 (TXA_2), a cyclo-oxygenase product of arachidonic acid, is a vasoconstrictive and platelet aggregating agent (Hamberg et al 1975). Platelet-activating factor (PAF) released from PMNs also belongs to recently characterized mediators of inflammation, being chemotactic for human PMNs both in-vitro (Czarnetzki & Benveniste 1981) and in-vivo (Archer et al 1985).

In our effort to find new compounds with biological activity, the extracts of the leaves of *Emblica officinalis* Gaertn were screened for their anti-inflammatory activity and an attempt was made to elucidate the possible mechanism of the found anti-inflammatory activity.

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Materials and methods

Identification of plant material. Leaves of *Emblica officinalis* Gaertn were collected from a wild tree not very far from the beach of Teluk Bahang, Penang Island. This plant had been identified by Mr Adenan Jaafar and voucher specimens deposited in the herbarium of the School of Biological Sciences, Universiti Sains, Malaysia.

Extraction. Leaves (3·6 kg) with their petioles were oven dried at 40°C for 48 h and 1·15 kg dried leaves obtained. They were then pulverized and extracted with petroleum ether (bp 60–80°C; BDH Ltd, Poole, UK). The marc was then extracted with methanol (James Burrough (FAD) Ltd, Essex, UK), followed by partition of the methanol extract between chloroform (BDH Ltd) and water. Each fraction of the extract was evaporated to dryness under reduced pressure and freeze-dried. Petroleum ether, methanol, chloroform and water extracts obtained were 25·7, 232, 5 and 54·5 g, respectively.

Anti-inflammatory evaluation. Groups of 6–12 fasted Sprague-Dawley rats, 150–200 g, were treated orally with either the extracts 2 g kg^{-1}, phenylbutazone (Sigma Chemical Co., St Louis, MO, USA) 15 mg kg^{-1} as positive control, or 1% acacia (Halewood Chemicals Ltd, Middlesex, UK) in 0·9% NaCl (saline) as a negative control. The test extracts and phenylbutazone were suspended in 1% acacia. One hour later, oedema, in the hind paw was induced by a subplantar injection of 0·1 mL of either freshly prepared 2% w/v carrageenan (Sigma Chemical Co.) or 0·12% w/v dextran (Sigma Chemical Co.).

The volume of the hind paw was measured by a mercury plethysmograph (Winter et al 1962). The plethysmometric measurement of the volume of the paws was made before and 3 h after administration of the inflammatory agent. Oedema volume (mL) and the inflammation percentage (oedema volume/control paw volume before inflammatory agent administration × 100) was calculated for each animal. Mean oedema volume increases were $3·80 \pm 0·28$ mL for carrageenan- and $1·70 \pm 0·49$ mL for dextran-induced rat hind paw inflammation (mean ± s.e.m.).

Isolation of polymorphonuclear leucocytes (PMNs). Blood was collected by venipuncture from healthy volunteers who had abstained from any drugs for at least one week before sampling. A buffy coat preparation of citrated blood was layered on Ficoll-Paque (Pharmacia Fine Chemicals AB, Uppsala, Sweden) and centrifuged (Bøyum 1976). Red cells were removed by dextran sedimentation followed by lysis of the remaining erythrocytes with Tris-buffered 0·15 M NH_4Cl. PMNs were washed twice with Dulbecco's phosphate-buffered saline (DPBS). After isolation the viability of PMNs was >98% as assessed by trypan blue exclusion (Mishell & Shiigi 1980) and mononuclear cell contamination was <2%.

PMN migration assay. Migration was measured using a modification of a double filter system in blind well-type chambers utilizing ^{51}Cr ($[^{51}Cr]Na_2CrO_4$; Amersham International, Buckinghamshire, UK) -labelled human PMNs (Gallin et al 1973; Kankaanranta et al 1991). The water fraction of the methanol extract, dissolved in saline, was added to the cells (5×10^6 mL^{-1})

10 min before commencement of the migration assay. *N*-Formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP, 10 nM; Sigma Chemical Co.) and LTB_4 (60 nM; Cayman Chemicals Co., Ann Arbor, MI, USA) were used as migration inducing agents. After incubation for 90 min, random migration was $6{\cdot}0 \pm 1{\cdot}0\%$, mean ± s.e.m., and migration in control experiments with LTB_4 and FMLP was $21{\cdot}0 \pm 2{\cdot}3$ and $21{\cdot}5 \pm 3{\cdot}4\%$, respectively. Experiments were run in triplicate.

LTB_4 and PAF assays. PMNs (1×10^7) were suspended in 1 mL DPBS and incubated at 37°C for 10 min. The water fraction of the methanol extract was dissolved in saline immediately before use and an aliquot (25 μL) added to the incubate to give final concentrations of 0·1–1000 μg mL^{-1}. Cells were then incubated for an additional 10 min before the mediator synthesis was induced by addition of Ca^{2+}-ionophore A23187 (1·0 μM; Calbiochem, San Diego, CA, USA). Cells were pelletted by centrifugation (10 000 *g* for 30 s at room temperature (21°C)) after 10 min incubation. LTB_4 concentrations in the incubate were measured with HPLC as previously described (Moilanen et al 1988). The PAF content of the cell pellet was measured by a bioassay based on [^{3}H]5-HT release from rabbit platelets after purification with TLC (Grandel et al 1985; Chang et al 1987). Stimulated PMNs produced LTB_4 $4{\cdot}9 \pm 0{\cdot}6$ ng/10^6 cells and PAF $19{\cdot}5 \pm 2{\cdot}5$ ng/10^6 cells, mean ± s.e.m. Experiments were run in duplicate.

Thromboxane B_2 (TXB_2) assay. Blood was drawn by venipuncture from healthy volunteers who had abstained from any drugs for two weeks. The blood was immediately mixed with the extract dissolved in saline and allowed to clot at 37°C for 30 min and cooled in an ice-bath for 10 min. Thereafter, serum was separated by centrifugation (900 *g*, 15 min, 4°C), immediately frozen and stored at −20°C for less than eight weeks before RIA. Thromboxane B_2, a metabolite of TXA_2, was measured in diluted serum by RIA (Seppälä et al 1984). Antiserum was received from Professor C. Taube, Martin Luther University, Halle, Germany, and the cross reactivity for other prostaglandins and metabolites was less than 0·1% with the exceptions of PGD_2 and PGE_2 (3·8 and 1·3%, respectively (Mest et al 1982)). The control level of TXB_2 was 298 ± 17 ng mL^{-1}, mean ± s.e.m. Experiments were run in duplicate.

Statistical analysis. Analysis of variance was made on the results for each group of animals, after verification by Bartlett's test that the results were normally distributed. The homogeneity of groups was verified by Duncan's test at an alpha level equal to 5%. In the chemotaxis assay the concentration of the water fraction of the methanol extract inducing 50% inhibition (IC50) was calculated on the basis of a semi-logarithmic dose-response curve in each experiment. Analysis of variance was used when the drug effects on LTB_4- and FMLP-induced chemotaxis were compared. The statistics were performed on the original data.

Results

In the anti-inflammatory study using carrageenan-induced oedema (Table 1) the water fraction of the methanol extract of *Emblica officinalis* Gaertn and phenylbutazone significantly ($P < 0{\cdot}01$ and $< 0{\cdot}001$, respectively) inhibited oedema formation. The methanol extract showed a clear tendency to reduce the hind paw swelling ($P = 0{\cdot}057$). The chloroform fraction of methanol extract did not influence carrageenan-induced inflammation. The water fraction of the methanol extract as well as phenylbutazone also inhibited dextran-induced oedema (Table 1; $P < 0{\cdot}05$).

The water fraction of the methanol extract, which was active in carrageenan- and dextran-induced inflammation, inhibited neither LTB_4 nor PAF synthesis in isolated human PMNs. It was not able to inhibit TXB_2 synthesis in human platelets during clotting (Table 2). On the other hand, it was a very potent inhibitor of human PMN migration induced by LTB_4 or FMLP (IC50 values $11{\cdot}6 \pm 4{\cdot}3$ and $9{\cdot}5 \pm 3{\cdot}1$ μg mL^{-1}, mean ± s.e.m., respectively) (Fig. 1). The dose-response curves of the water fraction of the methanol extract of *Emblica officinalis* Gaertn for LTB_4- and FMLP-induced migration did not differ significantly from each other (assessed by analysis of variance). Using trypan blue exclusion, cell death was eliminated as a possible contributing factor.

Table 1. The effects of orally administered *Emblica officinalis* Gaertn methanol extract, its water and chloroform fractions and phenylbutazone on carrageenan- or dextran-induced rat paw oedema. Each value is mean ± s.e.m. of 6–12 experiments or 8 experiments, respectively.

	Paw oedema (mL)	
	Carageenan-induced	Dextran-induced
Saline	$3{\cdot}80 \pm 0{\cdot}28$	$1{\cdot}70 \pm 0{\cdot}49$
Phenylbutazone (15 mg kg^{-1})	$2{\cdot}20 \pm 0{\cdot}26$***	$0{\cdot}36 \pm 0{\cdot}11$*
Methanol extract (2 g kg^{-1}) of *Emblica officinalis*	$2{\cdot}93 \pm 0{\cdot}33$	—
Water fraction (2 g kg^{-1})	$2{\cdot}25 \pm 0{\cdot}38$**	$0{\cdot}44 \pm 0{\cdot}14$*
Chloroform fraction (2 g kg^{-1})	$4{\cdot}16 \pm 0{\cdot}41$	—

* $P < 0{\cdot}05$, ** $P < 0{\cdot}01$ and *** $P < 0{\cdot}001$ as assessed by analysis of variance.

Table 2. The effects of the water fraction of the methanol extract of *Emblica officinalis* Gaertn on LTB_4 (ng/10^6 cells) and PAF (ng/10^6 cells) synthesis in isolated human PMNs and on TXB_2 (ng mL^{-1}) production in human platelets during blood clotting. Each value is mean ± s.e.m. of 2–5 experiments.

Emblica officinalis (μg mL^{-1})	Synthesis of		
	LTB_4	PAF	TXB_2
0	$4{\cdot}9 \pm 0{\cdot}6$	$19{\cdot}5 \pm 2{\cdot}5$	298 ± 17
0·1	$5{\cdot}1 \pm 0{\cdot}6$	$16{\cdot}0 \pm 0{\cdot}4$	—
1·0	$5{\cdot}2 \pm 0{\cdot}7$	$15{\cdot}8 \pm 0{\cdot}5$	—
10	$5{\cdot}0 \pm 1{\cdot}0$	$16{\cdot}3 \pm 0{\cdot}5$	294 ± 33
100	$5{\cdot}5 \pm 0{\cdot}6$	$27{\cdot}0 \pm 4{\cdot}0$	331 ± 49
500	—	$32{\cdot}1 \pm 4{\cdot}2$	312 ± 30
1000	—	$31{\cdot}3 \pm 3{\cdot}4$	243 ± 21

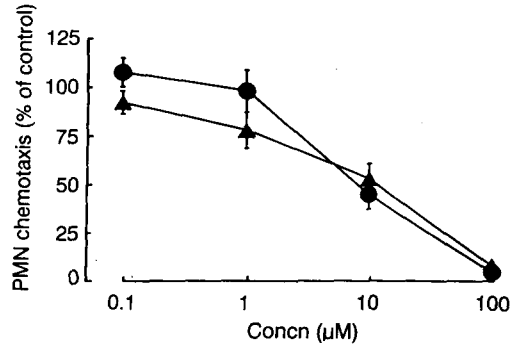

FIG. 1. The effects of the water fraction of the methanol extract of *Emblica officinalis* Gaertn on leukotriene B_4- (▲) and FMLP (●) -induced human polymorphonuclear leucocyte migration. Each value is mean ± s.e.m. of six experiments.

Discussion

The inhibition of carrageenan- and dextran-induced oedema by the water fraction of the methanol extract of *Emblica officinalis* Gaertn supports the concept that this plant has anti-inflammatory activities, as suggested in the traditional medicine of far-eastern peoples. It also indicates that the active component is relatively polar, since no anti-inflammatory activity was found in the chloroform fraction of the methanol extract.

The mechanism of the anti-inflammatory action of the water fraction of the methanol extract was studied using isolated human PMNs. It was found not to inhibit thromboxane, leukotriene or PAF synthesis in in-vitro conditions up to 1 mg mL^{-1} (for leukotriene synthesis up to 100 $\mu g\ mL^{-1}$) which approximates the highest concentration that could be achieved in in-vivo experiments, if the substance was fully absorbed and equally distributed in the rat. It seems that the anti-inflammatory action of this extract is different from that of conventional non-steroidal anti-inflammatory drugs (NSAIDs). Acetylsalicylic acid and most other NSAIDs are known to inhibit prostaglandin synthesis (for review see Abramson & Weissman 1989), but have no effect on leukotriene synthesis (Higgs & Flower 1981) or chemotaxis in human PMNs (Pecoud et al 1980; Kankaanranta et al 1991), while tolfenamic acid inhibits both prostaglandin and leukotriene synthesis (Moilanen et al 1988) as well as PMN migration (Kankaanranta et al 1991).

However, it was found that the water fraction of the methanol extract of *Emblica officinalis* Gaertn possesses marked anti-migration activity, the IC50 being around 10 $\mu g\ mL^{-1}$ for both LTB_4- and FMLP-induced PMN migration. Considering that this is only a crude extract, the active compound must be assumed to have a much lower IC50 value.

Our results suggest that the main anti-inflammatory mechanism of this extract is through its antimigration activity, and it does not influence the production of lipid mediators either through cyclo-oxygenase or lipoxygenase pathways. Carrageenan- and dextran-induced oedema are models of acute inflammation associated with vascular effects due to local inflammatory mediators without marked PMN influx. The anti-inflammatory action of *Emblica officinalis* Gaertn might thus be more pronounced in inflammatory reactions which merely depend on leucocyte influx.

The chemical compounds so far isolated from the leaves of this plant are polyphenolic constituents (gallic acid, ellagic acid, chebulic acid, chebulagic acid, chebulinic acid (Theresa et al 1965)) and a gallotannin, amlaic acid (Theresa et al 1967), and alkaloids, phyllantidine and phyllantine (Khanna & Bansal 1975). The fruit of *Emblica officinalis* Gaertn has been reported to contain ascorbic acid (Damodaran & Srinivasan 1935), phyllemblic acid and a phenolic compound, emblicol (Pillay & Mahadeva Iyer 1958). None of these compounds, as far as we know, could explain completely the antichemotactic or anti-inflammatory activity. However, a mixture of tannins isolated from the bark of *Anacardium occidentale* L. has been reported to have anti-inflammatory activity in carrageenan- and dextran-induced rat paw oedema and to inhibit the migration of leucocytes to an inflammatory site (Mota et al 1985).

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Book Review

Murder, Magic and Medicine
J. Mann
Published 1992 Oxford University Press, Oxford
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Murder, magic and mystery! Three subjects that have arguably exercised the imagination from the time of Cain, if not from Adam. This book reveals how Man has taken the things around him and improved, adapted or formulated them to make himself more murderous, more magical, and more immortal; that is, it is a book about the chemistry and pharmacology of natural products.

The book begins with the incantation of the three witches in the opening scene of 'Macbeth' and the author's own opening words are: 'This is probably the best-known potion in the English language. But did it work?' This opening beautifully epitomizes the book and its contents and the author's approach; a description of the weirdest collection of active concoctions imaginable, a healthy scepticism over their various claims, but a willingness to investigate the possibility that they did indeed work for sound scientific reasons.

The murder section deals with poisons. At least there is plenty of evidence that these worked. Indeed, given the plethora of available material, the lethality of quite easily obtained constituents and the propensity of Man throughout the ages to harbour grudges and pursue murderous feuds, it is a miracle that there are any of us left around to read about such things. Not all Professor Mann's poisons are used for murder—for example, the calamitous interaction of alcohol with the otherwise harmless ink-cap mushroom—although it is not hard to see them featuring in whodunits, fact or fiction.

The magic section is partly about the type of potion that Macbeth's witches brewed, probably highly poisonous concoctions with the power to raise spirits, foresee the future and bestow special powers. The incantations and atmospherics conspire to impress the victim rather than actually change anything. The main part of the section, however, is on the effect and mechanisms of mood-altering drugs, from the coca of the South American Indians to the flower power drugs of the 1960s and the Ecstasy of today. These drugs do not give men the power to fly, but they may make him think he can (with disastrous consequences) or they may simulate the experiences of flying.

The final chapter on medicine is the major part of the book with an emphasis on the discovery and development of drugs from natural sources. Unexpectedly, this I found was the least riveting part of the book, possibly because much of the anecdotal material on the discovery of today's drugs tends to be well-known in pharmaceutical circles and there was less of the 'fancy that' surprise in this section. Nevertheless, the author has written it in such a way that the reader may well be stimulated to follow up some of these stories, although the lack of modern references would make this difficult if he relied on this book as his only source.

The author makes a brave attempt to take the mystery out of chemical structures by representing compounds as 'three-dimensional' ball-and-stick models. However, this is not entirely successful; I found that I was mentally reconverting such structures to the conventional representation before I could make the comparisons suggested. I thought at first that the lay reader would not have this educational handicap, but on reflection I am inclined to think that anyone insufficiently versed in chemistry to be incapable of interpreting a chemical structure would be unlikely to be able to see the ball-and-stick models as solid objects and would be none the wiser.

As he began, the author finishes with a quote from a great English word-magician, W. S. Gilbert, while musing on the future and Man's ability to destroy the entire planet—"Man is Nature's sole mistake". Gilbert's character was talking about man rather than Man but it is a neat quote to end on.

It is a reviewer's prerogative to draw the author's attention to trivial mistakes and I would like to add mine. It was Gregory, not George, Pincus who did the pioneering endocrinology on the Pill, and the Gilbert quote above is from Princess Ida, not Ruddigore.

JOSEPH CHAMBERLAIN